

Exhibit 26



WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC MONOGRAPHS

ON THE

EVALUATION OF THE CARCINOGENIC
RISK OF CHEMICALS TO HUMANS

Silica and Some Silicates

VOLUME 42

IARC, LYON, FRANCE
1987



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ON THE
EVALUATION OF THE
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OF CHEMICALS TO HUMANS**

Silica and Some Silicates

VOLUME 42

This publication represents the views and expert opinions
of an IARC Working Group on the
Evaluation of the Carcinogenic Risk of Chemicals to Humans
which met in Lyon,

10-17 June 1986

1987

IARC MONOGRAPHS

In 1969, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic risk of chemicals to humans involving the production of critically evaluated monographs on individual chemicals. In 1980, the programme was expanded to include the evaluation of the carcinogenic risk associated with exposures to complex mixtures.

The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for chemicals and complex mixtures to which humans are known to be exposed, and on specific occupational exposures, to evaluate these data in terms of human risk with the help of international working groups of experts in chemical carcinogenesis and related fields, and to indicate where additional research efforts are needed.

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CONTENTS

NOTE TO THE READER	5
LIST OF PARTICIPANTS	7
PREAMBLE	
Background	13
Objective and Scope	13
Selection of Chemicals and Complex Mixtures for Monographs	14
Working Procedures	14
Data for Evaluations	15
The Working Group	15
General Principles	15
Explanatory Notes on the Monographs Contents	23
GENERAL REMARKS ON THE SUBSTANCES CONSIDERED	33
THE MONOGRAPHHS	
Silica	39
Wollastonite	145
Attapulgite	159
Sepiolite	175
Talc	185
Erionite	225
SUMMARY OF FINAL EVALUATIONS	243
GLOSSARY	247
CUMULATIVE CORRIGENDA TO VOLUMES 1-41	251
CUMULATIVE INDEX TO THE MONOGRAPHHS SERIES	265

NOTE TO THE READER

The term 'carcinogenic risk' in the *IARC Monographs* series is taken to mean the probability that exposure to the chemical will lead to cancer in humans.

Inclusion of a chemical in the *Monographs* does not imply that it is a carcinogen, only that the published data have been examined. Equally, the fact that a chemical has not yet been evaluated in a monograph does not mean that it is not carcinogenic.

Anyone who is aware of published data that may alter the evaluation of the carcinogenic risk of a chemical to humans is encouraged to make this information available to the Unit of Carcinogen Identification and Evaluation, International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 08, France, in order that the chemical may be considered for re-evaluation by a future Working Group.

Although every effort is made to prepare the monographs as accurately as possible, mistakes may occur. Readers are requested to communicate any errors to the Unit of Carcinogen Identification and Evaluation, so that corrections can be reported in future volumes.

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OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS:
SILICA AND SOME SILICATES**

Lyon, 10-17 June 1986

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IARC MONOGRAPHS VOLUME 42

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PREAMBLE

IARC MONOGRAPHS PROGRAMME ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS¹

PREAMBLE

1. BACKGROUND

In 1969, the International Agency for Research on Cancer (IARC) initiated a programme to evaluate the carcinogenic risk of chemicals to humans and to produce monographs on individual chemicals. Following the recommendations of an ad-hoc Working Group, which met in Lyon in 1979 to prepare criteria to select chemicals for *IARC Monographs*(1), the *Monographs* programme was expanded to include consideration of exposures to complex mixtures which may occur, for example, in many occupations or as a result of human habits.

The criteria established in 1971 to evaluate carcinogenic risk to humans were adopted by all the working groups whose deliberations resulted in the first 16 volumes of the *IARC Monographs* series. This preamble reflects subsequent re-evaluation of those criteria by working groups which met in 1977(2), 1978(3), 1982(4) and 1983(5).

2. OBJECTIVE AND SCOPE

The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for chemicals, groups of chemicals, industrial processes and other complex mixtures to which humans are known to be exposed, to evaluate the data in terms of human risk with the help of international working groups of experts, and to indicate where additional research efforts are needed. These evaluations are intended to assist national and international authorities in formulating decisions concerning preventive measures. No recommendation is given concerning legislation, since this depends on risk-benefit evaluations, which seem best made by individual governments and/or other international agencies.

¹This project is supported by PHS Grant No. 2 U01 CA33193-04 awarded by the US National Cancer Institute, Department of Health and Human Services.

The *IARC Monographs* are recognized as an authoritative source of information on the carcinogenicity of environmental and other chemicals. A users' survey, made in 1984, indicated that the monographs are consulted by various agencies in 45 countries. As of June 1987, 42 volumes of the *Monographs* had been published or were in press. Five supplements have been published: two summaries of evaluations of chemicals associated with human cancer, an evaluation of screening assays for carcinogens, and two cross indexes of synonyms and trade names of chemicals evaluated in the series(6).

3. SELECTION OF CHEMICALS AND COMPLEX EXPOSURES FOR MONOGRAPHS

The chemicals (natural and synthetic including those which occur as mixtures and in manufacturing processes) and complex exposures are selected for evaluation on the basis of two main criteria: (a) there is evidence of human exposure, and (b) there is some experimental evidence of carcinogenicity and/or there is some evidence or suspicion of a risk to humans. In certain instances, chemical analogues are also considered. The scientific literature is surveyed for published data relevant to the *Monographs* programme; and the IARC *Survey of Chemicals Being Tested for Carcinogenicity*(7) often indicates those chemicals that may be scheduled for future meetings.

As new data on chemicals for which monographs have already been prepared become available, re-evaluations are made at subsequent meetings, and revised monographs are published.

4. WORKING PROCEDURES

Approximately one year in advance of a meeting of a working group, a list of the substances or complex exposures to be considered is prepared by IARC staff in consultation with other experts. Subsequently, all relevant biological data are collected by IARC; recognized sources of information on chemical carcinogenesis and on-line systems such as CANCERLINE, MEDLINE and TOXLINE are used in conjunction with US Public Health Service Publication No. 149(8). Bibliographical sources for data on mutagenicity and teratogenicity are the Environmental Mutagen Information Center and the Environmental Teratology Information Center, both located at the Oak Ridge National Laboratory, TN, USA.

The major collection of data and the preparation of first drafts for the sections on chemical and physical properties, on production and use, on occurrence, and on analysis are carried out by Tracor Jitco, Inc., and its subcontractor, Technical Resources, Inc., both in Rockville, MD, USA, under a separate contract with the US National Cancer Institute. Most of the data so obtained refer to the USA and Japan; IARC attempts to supplement this information with that from other sources in Europe. Representatives from industrial associations may assist in the preparation of sections describing industrial processes.

Six months before the meeting, articles containing relevant biological data are sent to an expert(s), or are used by IARC staff, to prepare first drafts of the sections on biological effects. The complete drafts are then compiled by IARC staff and sent, prior to the meeting, to all participants of the Working Group for their comments.

PREAMBLE

15

The Working Group meets in Lyon for seven to eight days to discuss and finalize the texts of the monographs and to formulate the evaluations. After the meeting, the master copy of each monograph is verified by consulting the original literature, edited by a professional editor and prepared for reproduction. The aim is to publish monographs within nine months of the Working Group meeting. Each volume of monographs is printed in 4000 copies for distribution to governments, regulatory agencies and interested scientists. The monographs are also available *via* the WHO Distribution and Sales Service.

These procedures are followed for the preparation of most volumes of monographs, which cover chemicals and groups of chemicals; however, they may vary when the subject matter is an industry or life-style factor.

5. DATA FOR EVALUATIONS

With regard to biological data, only reports that have been published or accepted for publication are reviewed by the working groups, although a few exceptions have been made: in certain instances, reports from government agencies that have undergone peer review and are widely available are considered. The monographs do not cite all of the literature on a particular chemical or complex exposure: only those data considered by the Working Group to be relevant to the evaluation of carcinogenic risk to humans are included.

Anyone who is aware of data that have been published or are in press which are relevant to the evaluations of the carcinogenic risk to humans of chemicals or complex exposures for which monographs have appeared is asked to make them available to the Unit of Carcinogen Identification and Evaluation, International Agency for Research on Cancer, Lyon, France.

6. THE WORKING GROUP

The tasks of the Working Group are five-fold: (a) to ascertain that all data have been collected; (b) to select the data relevant for evaluation; (c) to ensure that the summaries of the data enable the reader to follow the reasoning of the Working Group; (d) to judge the significance of the results of experimental and epidemiological studies; and (e) to make an evaluation of the carcinogenicity of the chemical or complex exposure.

Working Group participants who contributed to the consideration and evaluation of chemicals or complex exposures within a particular volume are listed, with their addresses, at the beginning of each publication. Each member serves as an individual scientist and not as a representative of any organization or government. In addition, observers are often invited from national and international agencies and industrial associations.

7. GENERAL PRINCIPLES APPLIED BY THE WORKING GROUP IN EVALUATING CARCINOGENIC RISK OF CHEMICALS OR COMPLEX MIXTURES

The widely accepted meaning of the term 'chemical carcinogenesis', and that used in these monographs, is the induction by chemicals (or complex mixtures of chemicals) of

neoplasms that are not usually observed, the earlier induction of neoplasms that are commonly observed, and/or the induction of more neoplasms than are usually found—although fundamentally different mechanisms may be involved in these three situations. Etymologically, the term ‘carcinogenesis’ means the induction of cancer, that is, of malignant neoplasms; however, the commonly accepted meaning is the induction of various types of neoplasms or of a combination of malignant and benign tumours. In the monographs, the words ‘tumour’ and ‘neoplasm’ are used interchangeably. (In the scientific literature, the terms ‘tumorigen’, ‘oncogen’ and ‘blastomogen’ have all been used synonymously with ‘carcinogen’, although occasionally ‘tumorigen’ has been used specifically to denote a substance that induces benign tumours.)

(a) Experimental Evidence

(i) Evidence for carcinogenicity in experimental animals

The Working Group considers various aspects of the experimental evidence reported in the literature and formulates an evaluation of that evidence.

Qualitative aspects: Both the interpretation and evaluation of a particular study as well as the overall assessment of the carcinogenic activity of a chemical (or complex mixture) involve several considerations of qualitative importance, including: (a) the experimental parameters under which the chemical was tested, including route of administration and exposure, species, strain, sex, age, etc.; (b) the consistency with which the chemical has been shown to be carcinogenic, e.g., in how many species and at which target organ(s); (c) the spectrum of neoplastic response, from benign neoplasm to multiple malignant tumours; (d) the stage of tumour formation in which a chemical may be involved: some chemicals act as complete carcinogens and have initiating and promoting activity, while others may have promoting activity only; and (e) the possible role of modifying factors.

There are problems not only of differential survival but of differential toxicity, which may be manifested by unequal growth and weight gain in treated and control animals. These complexities are also considered in the interpretation of data.

Many chemicals induce both benign and malignant tumours. Among chemicals that have been studied extensively, there are few instances in which the only neoplasms induced are benign. Benign tumours may represent a stage in the evolution of a malignant neoplasm or they may be ‘end-points’ that do not readily undergo transition to malignancy. If a substance is found to induce only benign tumours in experimental animals, it should nevertheless be suspected of being a carcinogen, and it requires further investigation.

Hormonal carcinogenesis: Hormonal carcinogenesis presents certain distinctive features: the chemicals involved occur both endogenously and exogenously; in many instances, long exposure is required; and tumours occur in the target tissue in association with a stimulation of non-neoplastic growth, although in some cases hormones promote the proliferation of tumour cells in a target organ. For hormones that occur in excessive amounts, for hormone-mimetic agents and for agents that cause hyperactivity or imbalance in the endocrine system, evaluative methods comparable with those used to identify chemical carcinogens may be required; particular emphasis must be laid on quantitative

PREAMBLE

17

aspects and duration of exposure. Some chemical carcinogens have significant side effects on the endocrine system, which may also result in hormonal carcinogenesis. Synthetic hormones and anti-hormones can be expected to possess other pharmacological and toxicological actions in addition to those on the endocrine system, and in this respect they must be treated like any other chemical with regard to intrinsic carcinogenic potential.

Complex mixtures: There is an increasing amount of data from long-term carcinogenicity studies on complex mixtures and on crude materials obtained by sampling in occupational environments. The representativity of such samples must be considered carefully.

Quantitative aspects: Dose-response studies are important in the evaluation of carcinogenesis: the confidence with which a carcinogenic effect can be established is strengthened by the observation of an increasing incidence of neoplasms with increasing exposure.

The assessment of carcinogenicity in animals is frequently complicated by recognized differences among the test animals (species, strain, sex, age) and route and schedule of administration; often, the target organs at which a cancer occurs and its histological type may vary with these parameters. Nevertheless, indices of carcinogenic potency in particular experimental systems (for instance, the dose-rate required under continuous exposure to halve the probability of the animals remaining tumourless(9)) have been formulated in the hope that, at least among categories of fairly similar agents, such indices may be of some predictive value in other species, including humans.

Chemical carcinogens share many common biological properties, which include metabolism to reactive (electrophilic(10-11)) intermediates capable of interacting with DNA. However, they may differ widely in the dose required to produce a given level of tumour induction. The reason for this variation in dose-response is not understood, but it may be due to differences in metabolic activation and detoxification processes, in different DNA repair capacities among various organs and species or to the operation of qualitatively distinct mechanisms.

Statistical analysis of animal studies: It is possible that an animal may die prematurely from unrelated causes, so that tumours that would have arisen had the animal lived longer may not be observed; this possibility must be allowed for. Various analytical techniques have been developed which use the assumption of independence of competing risks to allow for the effects of intercurrent mortality on the final numbers of tumour-bearing animals in particular treatment groups.

For externally visible tumours and for neoplasms that cause death, methods such as Kaplan-Meier (i.e., 'life-table', 'product-limit' or 'actuarial') estimates(9), with associated significance tests(12), have been recommended. For internal neoplasms that are discovered 'incidentally'(12) at autopsy but that did not cause the death of the host, different estimates(13) and significance tests(12) may be necessary for the unbiased study of the numbers of tumour-bearing animals.

The design and statistical analysis of long-term carcinogenicity experiments were reviewed in Supplement 2 to the *Monographs* series(14). That review outlined the way in

which the context of observation of a given tumour (fatal or incidental) could be included in an analysis yielding a single combined result. This method requires information on time to death for each animal and is therefore comparable to only a limited extent with analyses which include global proportions of tumour-bearing animals.

Evaluation of carcinogenicity studies in experimental animals: The evidence of carcinogenicity in experimental animals is assessed by the Working Group and judged to fall into one of four groups, defined as follows:

- (1) *Sufficient evidence* of carcinogenicity is provided when there is an increased incidence of malignant tumours: (a) in multiple species or strains; or (b) in multiple experiments (preferably with different routes of administration or using different dose levels); or (c) to an unusual degree with regard to incidence, site or type of tumour, or age at onset. Additional evidence may be provided by data on dose-response effects.
- (2) *Limited evidence* of carcinogenicity is available when the data suggest a carcinogenic effect but are limited because: (a) the studies involve a single species, strain or experiment; or (b) the experiments are restricted by inadequate dosage levels, inadequate duration of exposure to the agent, inadequate period of follow-up, poor survival, too few animals, or inadequate reporting; or (c) the neoplasms produced often occur spontaneously and, in the past, have been difficult to classify as malignant by histological criteria alone (e.g., lung adenomas and adenocarcinomas and liver tumours in certain strains of mice).
- (3) *Inadequate evidence* of carcinogenicity is available when, because of major qualitative or quantitative limitations, the studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect.
- (4) *No evidence* of carcinogenicity applies when several adequate studies are available which show that, within the limits of the tests used, the chemical or complex mixture is not carcinogenic.

It should be noted that the categories *sufficient evidence* and *limited evidence* refer only to the strength of the experimental evidence that these chemicals or complex mixtures are carcinogenic and not to the extent of their carcinogenic activity nor to the mechanism involved. The classification of any chemical may change as new information becomes available.

(ii) *Evidence for activity in short-term tests¹*

Many short-term tests bearing on postulated mechanisms of carcinogenesis or on the properties of known carcinogens have been developed in recent years. The induction of cancer is thought to proceed by a series of steps, some of which have been distinguished experimentally (15-19). The first step — initiation — is thought to involve damage to DNA, resulting in heritable alterations in or rearrangements of genetic information. Most short-term tests in common use today are designed to evaluate the genetic activity of a substance.

¹Based on the recommendations of a working group which met in 1983(5).

PREAMBLE

19

Data from these assays are useful for identifying potential carcinogenic hazards, in identifying active metabolites of known carcinogens in human or animal body fluids, and in helping to elucidate mechanisms of carcinogenesis. Short-term tests to detect agents with tumour-promoting activity are, at this time, insufficiently developed.

Because of the large number of short-term tests, it is difficult to establish rigid criteria for adequacy that would be applicable to all studies. General considerations relevant to all tests, however, include (a) that the test system be valid with respect to known animal carcinogens and noncarcinogens; (b) that the experimental parameters under which the chemical (or complex mixture) is tested include a sufficiently wide dose range and duration of exposure to the agent and an appropriate metabolic system; (c) that appropriate controls be used; and (d) that the purity of the compound or, in the case of complex mixtures, that the source and representativity of the sample being tested be specified. Confidence in positive results is increased if a dose-response relationship is demonstrated and if this effect has been reported in two or more independent studies.

Most established short-term tests employ as end-points well-defined genetic markers in prokaryotes and lower eukaryotes and in mammalian cell lines. The tests can be grouped according to the end-point detected:

Tests of *DNA damage*. These include tests for covalent binding to DNA, induction of DNA breakage or repair, induction of prophage in bacteria and differential survival of DNA repair-proficient/-deficient strains of bacteria.

Tests of *mutation* (measurement of heritable alterations in phenotype and/or genotype). These include tests for detection of the loss or alteration of a gene product, and change of function through forward or reverse mutation, recombination and gene conversion; they may involve the nuclear genome, the mitochondrial genome and resident viral or plasmid genomes.

Tests of *chromosomal effects*. These include tests for detection of changes in chromosome number (aneuploidy), structural chromosomal aberrations, sister chromatid exchanges, micronuclei and dominant-lethal events. This classification does not imply that some chromosomal effects are not mutational events.

Tests for *cell transformation*, which monitor the production of preneoplastic or neoplastic cells in culture, are also of importance because they attempt to simulate essential steps in cellular carcinogenesis. These assays are not grouped with those listed above since the mechanisms by which chemicals induce cell transformation may not necessarily be the result of genetic change.

The selection of specific tests and end-points for consideration remains flexible and should reflect the most advanced state of knowledge in this field.

The data from short-term tests are summarized by the Working Group and the test results tabulated according to the end-points detected and the biological complexities of the test systems. The format of the table used is shown below. In these tables, a '+' indicates that the compound was judged by the Working Group to be significantly positive in one or more assays for the specific end-point and level of biological complexity; '-' indicates that it was judged to be negative in one or more assays; and '?' indicates that there were contradictory

results from different laboratories or in different biological systems, or that the result was judged to be equivocal. These judgements reflect the assessment by the Working Group of the quality of the data (including such factors as the purity of the test compound, problems of metabolic activation and appropriateness of the test system) and the relative significance of the component tests.

Overall assessment of data from short-term tests

Genetic activity	Cell transformation		
	DNA damage	Mutation	Chromosomal effects
Prokaryotes			
Fungi/ Green plants			
Insects			
Mammalian cells (<i>in vitro</i>)			
Mammals (<i>in vivo</i>)			
Humans (<i>in vivo</i>)			

An overall assessment of the evidence for *genetic activity* is then made on the basis of the entries in the table, and the evidence is judged to fall into one of four categories, defined as follows:

- (1) *Sufficient evidence* is provided by at least three positive entries, one of which must involve mammalian cells *in vitro* or *in vivo* and which must include at least two of three end-points — DNA damage, mutation and chromosomal effects.
- (2) *Limited evidence* is provided by at least two positive entries.
- (3) *Inadequate evidence* is available when there is only one positive entry or when there are too few data to permit an evaluation of an absence of genetic activity or when there are unexplained, inconsistent findings in different test systems.

PREAMBLE

21

(4) *No evidence* applies when there are only negative entries; these must include entries for at least two end-points and two levels of biological complexity, one of which must involve mammalian cells *in vitro* or *in vivo*.

It is emphasized that the above definitions are operational, and that the assignment of a chemical or complex mixture into one of these categories is thus arbitrary.

In general, emphasis is placed on positive results; however, in view of the limitations of current knowledge about mechanisms of carcinogenesis, certain cautions should be respected: (i) At present, short-term tests should not be used by themselves to conclude whether or not an agent is carcinogenic nor can they predict reliably the relative potencies of compounds as carcinogens in intact animals. (ii) Since the currently available tests do not detect all classes of agents that are active in the carcinogenic process (e.g., hormones), one must be cautious in utilizing these tests as the sole criterion for setting priorities in carcinogenesis research and in selecting compounds for animal bioassays. (iii) Negative results from short-term tests cannot be considered as evidence to rule out carcinogenicity, nor does lack of demonstrable genetic activity attribute an epigenetic or any other property to a substance (5).

(b) Evaluation of Carcinogenicity in Humans

Evidence of carcinogenicity can be derived from case reports, descriptive epidemiological studies and analytical epidemiological studies.

An analytical study that shows a positive association between an exposure and a cancer may be interpreted as implying causality to a greater or lesser extent, on the basis of the following criteria: (a) There is no identifiable positive bias. (By ‘positive bias’ is meant the operation of factors in study design or execution that lead erroneously to a more strongly positive association between an exposure and disease than in fact exists. Examples of positive bias include, in case-control studies, better documentation of the exposure for cases than for controls, and, in cohort studies, the use of better means of detecting cancer in exposed individuals than in individuals not exposed.) (b) The possibility of positive confounding has been considered. (By ‘positive confounding’ is meant a situation in which the relationship between an exposure and a disease is rendered more strongly positive than it truly is as a result of an association between that exposure and another exposure which either causes or prevents the disease. An example of positive confounding is the association between coffee consumption and lung cancer, which results from their joint association with cigarette smoking.) (c) The association is unlikely to be due to chance alone. (d) The association is strong. (e) There is a dose-response relationship.

In some instances, a single epidemiological study may be strongly indicative of a cause-effect relationship; however, the most convincing evidence of causality comes when several independent studies done under different circumstances result in ‘positive’ findings.

Analytical epidemiological studies that show no association between an exposure and a cancer (‘negative’ studies) should be interpreted according to criteria analogous to those listed above: (a) there is no identifiable negative bias; (b) the possibility of negative confounding has been considered; and (c) the possible effects of misclassification of exposure or outcome have been weighed. In addition, it must be recognized that the

probability that a given study can detect a certain effect is limited by its size. This can be perceived from the confidence limits around the estimate of association or relative risk. In a study regarded as ‘negative’, the upper confidence limit may indicate a relative risk substantially greater than unity; in that case, the study excludes only relative risks that are above the upper limit. This usually means that a ‘negative’ study must be large to be convincing. Confidence in a ‘negative’ result is increased when several independent studies carried out under different circumstances are in agreement. Finally, a ‘negative’ study may be considered to be relevant only to dose levels within or below the range of those observed in the study and is pertinent only if sufficient time has elapsed since first human exposure to the agent. Experience with human cancers of known etiology suggests that the period from first exposure to a chemical carcinogen to development of clinically observed cancer is usually measured in decades and may be in excess of 30 years.

The evidence for carcinogenicity from studies in humans is assessed by the Working Group and judged to fall into one of four groups, defined as follows:

- (1) *Sufficient evidence* of carcinogenicity indicates that there is a causal relationship between the exposure and human cancer.
- (2) *Limited evidence* of carcinogenicity indicates that a causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding, could not adequately be excluded.
- (3) *Inadequate evidence* of carcinogenicity, which applies to both positive and negative evidence, indicates that one of two conditions prevailed: (a) there are few pertinent data; or (b) the available studies, while showing evidence of association, do not exclude chance, bias or confounding.
- (4) *No evidence* of carcinogenicity applies when several adequate studies are available which do not show evidence of carcinogenicity.

(c) Relevance of Experimental Data to the Evaluation of Carcinogenic Risk to Humans

Information compiled from the first 41 volumes of the *IARC Monographs* shows that, of the chemicals or groups of chemicals now generally accepted to cause or probably to cause cancer in humans, all of those that have been tested appropriately produce cancer in at least one animal species. For several of the chemicals (e.g., aflatoxins, 4-aminobiphenyl, diethylstilboestrol, melphalan, mustard gas and vinyl chloride), evidence of carcinogenicity in experimental animals preceded evidence obtained from epidemiological studies or case reports.

For many of the chemicals (or complex mixtures) evaluated in the *IARC Monographs* for which there is *sufficient evidence* of carcinogenicity in animals, data relating to carcinogenicity for humans are either insufficient or nonexistent. **In the absence of adequate data on humans, it is reasonable, for practical purposes, to regard chemicals or exposures for which there is sufficient evidence of carcinogenicity in animals as if they presented a carcinogenic risk to humans.** The use of the expressions ‘for practical purposes’ and ‘as if they presented a carcinogenic risk’ indicates that, at the present time, a correlation between

PREAMBLE

23

carcinogenicity in animals and possible human risk cannot be made on a purely scientific basis, but only pragmatically. Such a pragmatic correlation may be useful to regulatory agencies in making decisions related to the primary prevention of cancer.

In the present state of knowledge, it would be difficult to define a predictable relationship between the dose (mg/kg bw per day) of a particular chemical required to produce cancer in test animals and the dose that would produce a similar incidence of cancer in humans. Some data, however, suggest that such a relationship may exist(20,21), at least for certain classes of carcinogenic chemicals, although no acceptable method is currently available for quantifying the possible errors that may be involved in such an extrapolation procedure.

8. EXPLANATORY NOTES ON THE CONTENTS OF MONOGRAPHS ON CHEMICALS AND COMPLEX MIXTURES

These notes apply to the format of most monographs, except for those that address industries or life-style factors. Thus, sections 1 and 2, as described below, are applicable in monographs on chemicals or groups of chemicals; in other monographs, they may be replaced by sections on the history of an industry or habit, a description of a process and other relevant information.

(a) Chemical and Physical Data (Section 1)

The Chemical Abstracts Services Registry Number, the Chemical Abstracts Primary Name (Ninth Collective Index)(22) and the IUPAC Systematic Name(23) are recorded in section 1. Other synonyms and trade names are given, but the list is not necessarily comprehensive. Some of the trade names may be those of mixtures in which the compound being evaluated is only one of the ingredients.

The structural and molecular formulae, molecular weight and chemical and physical properties are given. The properties listed refer to the pure substance, unless otherwise specified, and include, in particular, data that might be relevant to identification, environmental fate and human exposure, and biological effects, including carcinogenicity.

A separate description of the composition of technical products includes available information on impurities and formulated products.

(b) Production, Use, Occurrence and Analysis (Section 2)

The purpose of section 2 is to provide indications of the extent of past and present human exposure to the chemical.

Monographs on occupational exposures to complex mixtures or exposures to complex mixtures resulting from human habits include sections on: historical perspectives; description of the industry or habit; manufacturing processes and use patterns; exposures in the workplace; chemistry of the complex mixture.

(i) *Synthesis*

Since cancer is a delayed toxic effect, the dates of first synthesis and of first commercial production of the chemical are provided. This information allows a reasonable estimate to be made of the date before which no human exposure could have occurred. In addition, methods of synthesis used in past and present commercial production are described.

(ii) *Production*

Since Europe, Japan and the USA are reasonably representative industrialized areas of the world, most data on production, foreign trade and uses are obtained from those regions. It should not, however, be inferred that those areas or nations are the sole or even necessarily the major sources or users of any individual chemical.

Production and foreign trade data are obtained from both governmental and trade publications. In some cases, separate production data on organic chemicals manufactured in the USA are not available because their publication could disclose confidential information. In such cases, an indication of the minimum quantity produced can be inferred from the number of companies reporting commercial production. Each company is required to report on individual chemicals if the annual sales value or production volume exceeds a specified minimum level. These levels vary for chemicals classified for different uses, e.g., medicinals and plastics; in fact, the minimal reportable level for annual sales value ranges from \$1000-\$50 000, and the minimal reportable level for annual production volume ranges from 450-22 700 kg for different classes of use. Data on production are also obtained by means of general questionnaires sent to companies thought to produce the compounds being evaluated. Information from the completed questionnaires is compiled, by country, and the resulting estimates of production are included in the individual monographs.

(iii) *Use*

Information on uses is usually obtained from published sources but is often complemented by direct contact with manufacturers. Some uses identified may not be current or major applications, and the coverage is not necessarily comprehensive. In the case of drugs, mention of their therapeutic uses does not necessarily represent current practice nor does it imply judgement as to their clinical efficacy.

Statements concerning regulations, standards and guidelines (e.g., pesticide registrations, maximum levels permitted in foods, occupational standards and allowable limits) in specific countries may not reflect the most recent situation, since such standards are continuously reviewed and modified. The absence of information on regulatory status for a country should not be taken to imply that that country does not have regulations with regard to the chemical.

(iv) *Occurrence*

Information on the occurrence of a chemical in the environment is obtained from published data, including that derived from the monitoring and surveillance of levels of the chemical in occupational environments, air, water, soil, foods and tissues of animals and humans. When no published data are available to the Working Group, unpublished reports,

PREAMBLE

25

deemed appropriate, may be considered. When available, data on the generation, persistence and bioaccumulation of a chemical are also included.

(v) *Analysis*

The purpose of the section on analysis is to give the reader an overview, rather than a complete list, of current methods cited in the literature. No critical evaluation or recommendation of any of the methods is meant or implied.

(c) Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans (Section 3)

In general, the data recorded in section 3 are summarized as given by the author; however, comments made by the Working Group on certain shortcomings of reporting, of statistical analysis or of experimental design are given in square brackets. The nature and extent of impurities/contaminants in the chemicals being tested are given when available.

(i) *Carcinogenicity studies in animals*

The monographs are not intended to cover all reported studies. A few studies are purposely omitted because they are inadequate (e.g., too short a duration, too few animals, poor survival) or because they are judged irrelevant for the purpose of the evaluation. In certain cases, however, such studies are mentioned briefly, particularly when the information is considered to be a useful supplement to other reports or when it is the only data available. Their inclusion does not, however, imply acceptance of the adequacy of their experimental design or of the analysis and interpretation of their results.

Mention is made of all routes of administration by which the test material has been adequately tested and of all species in which relevant tests have been done(24). In most cases, animal strains are given. Quantitative data are given to indicate the order of magnitude of the effective carcinogenic doses. In general, the doses and schedules are indicated as they appear in the original report; sometimes units have been converted for easier comparison. Experiments in which the compound was administered in conjunction with known carcinogens and experiments on factors that modify the carcinogenic effect are also reported. Experiments on the carcinogenicity of known metabolites and derivatives are also included.

(ii) *Other relevant biological data*

LD_{50} data are given when available, and other data on toxicity are included when considered relevant.

Data on effects on reproduction, on teratogenicity and embryo- and fetotoxicity and on placental transfer, from studies in experimental animals and from observations in humans, are included when considered relevant.

Information is given on absorption, distribution and excretion. Data on metabolism are usually restricted to studies that show the metabolic fate of the chemical in experimental animals and humans, and comparisons of data from animals and humans are made when possible.

Data from short-term tests are also included. In addition to the tests for genetic activity and cell transformation described previously (see pages 18-19), data from studies of related effects, but for which the relevance to the carcinogenic process is less well established, may also be mentioned.

The criteria used for considering short-term tests and for evaluating their results have been described (see pages 19-21). In general, the authors' results are given as reported. An assessment of the data by the Working Group which differs from that of the authors, and comments concerning aspects of the study that might affect its interpretation are given in square brackets. Reports of studies in which few or no experimental details are given, or in which the data on which a reported positive or negative result is based are not available for examination, are cited, but are identified as 'abstract' or 'details not given' and are not considered in the summary tables or in making the overall assessment of genetic activity.

For several recent reviews on short-term tests, see IARC(24), Montesano *et al.*(25), de Serres and Ashby(26), Sugimura *et al.*(27), Bartsch *et al.*(28) and Hollstein *et al.*(29).

(iii) Case reports and epidemiological studies of carcinogenicity to humans

Observations in humans are summarized in this section. These include case reports, descriptive epidemiological studies (which correlate cancer incidence in space or time to an exposure) and analytical epidemiological studies of the case-control or cohort type. In principle, a comprehensive coverage is made of observations in humans; however, reports are excluded when judged to be clearly not pertinent. This applies in particular to case reports, in which either the clinico-pathological description of the tumours or the exposure history, or both, are poorly described; and to published routine statistics, for example, of cancer mortality by occupational category, when the categories are so broadly defined as to contribute virtually no specific information on the possible relation between cancer occurrence and a given exposure. Results of studies are assessed on the basis of the data and analyses that are presented in the published papers. Some additional analyses of the published data may be performed by the Working Group to gain better insight into the relation between cancer occurrence and the exposure under consideration. The Working Group may use these analyses in its assessment of the evidence or may actually include them in the text to summarize a study; in such cases, the results of the supplementary analyses are given in square brackets. Any comments by the Working Group are also reported in square brackets; however, these are kept to a minimum, being restricted to those instances in which it is felt that an important aspect of a study, directly impinging on its interpretation, should be brought to the attention of the reader.

(d) Summary of Data Reported and Evaluation (Section 4)

Section 4 summarizes the relevant data from animals and humans and gives the critical views of the Working Group on those data.

(i) Exposures

Human exposure to the chemical or complex mixture is summarized on the basis of data on production, use and occurrence.

PREAMBLE

27

(ii) *Experimental data*

Data relevant to the evaluation of the carcinogenicity of the test material in animals are summarized in this section. The animal species mentioned are those in which the carcinogenicity of the substance was clearly demonstrated. Tumour sites are also indicated. If the substance has produced tumours after prenatal exposure or in single-dose experiments, this is indicated. Dose-response data are given when available.

Significant findings on effects on reproduction and prenatal toxicity, and results from short-term tests for genetic activity and cell transformation assays are summarized, and the latter are presented in tables. An overall assessment is made of the degree of evidence for genetic activity in short-term tests.

(iii) *Human data*

Case reports and epidemiological studies that are considered to be pertinent to an assessment of human carcinogenicity are described. Other biological data that are considered to be relevant are also mentioned.

(iv) *Evaluation*

This section comprises evaluations by the Working Group of the degrees of evidence for carcinogenicity of the exposure to experimental animals and to humans. An overall evaluation is then made of the carcinogenic risk of the chemical or complex mixture to humans. This section should be read in conjunction with pages 18 and 22 of this Preamble for definitions of degrees of evidence.

When no data are available from epidemiological studies but there is *sufficient evidence* that the exposure is carcinogenic to animals, a footnote is included, reading: 'In the absence of adequate data on humans, it is reasonable, for practical purposes, to regard chemicals or exposures for which there is *sufficient evidence* of carcinogenicity in animals as if they presented a carcinogenic risk to humans' (see pp. 22-23 of this Preamble).

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PREAMBLE

29

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31

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GENERAL REMARKS ON THE SUBSTANCES CONSIDERED

Minerals considered

This forty-second volume of the *IARC Monographs* comprises six monographs: one on silica and five on silicate minerals. Asbestos, which was evaluated by previous working groups (IARC, 1973, 1977, 1982), was not considered in this volume.

Silica is the name given to minerals that are composed of silicon dioxide (SiO_2); they occur naturally in both crystalline and amorphous forms. Three crystalline, polymorphic forms are relevant to human health: quartz, tridymite and cristobalite. The amorphous form is often biogenic and is the common silica phase of diatomite. Vitreous and fused silicas are produced by high-temperature treatment of silica-containing materials. Quartz is by far the most common form of SiO_2 , and it is one of the most abundant minerals in the Earth's crust. Most exposures described as being to 'free silica' are to this form of SiO_2 .

Natural *wollastonite* is a calcium metasilicate used as a filler in paints and in plastics, as a component of ceramic melts and as an abrasive. Consumers are usually exposed to altered forms of this mineral. Synthetic forms of calcium silicate are not considered in this volume.

Attapulgite (palygorskite) is a fibrous clay mineral. Its structure, chemistry and physical form are similar to those of sepiolite, as both minerals are members of the paramontmorillonite-sepiolite series. Its uses include that of filler, sorbent and excipient. Consumers may be exposed to powders such as those found in pet litter.

Sepiolite is the magnesium end-member of the fibrous clays belonging to the paramontmorillonite-sepiolite group. Its uses are similar to those of attapulgite.

Talc is classified by its structure and chemistry. The name 'talc' is used in industry and by the general public to describe a range of powders derived from ground rocks containing varying proportions of talc. The quality and type of minerals of which industrial-grade talc powders are composed vary widely; some may contain considerable amounts of amphibole minerals in a range of habits, including acicular cleavage fragments and asbestosiform fibres.

Erionite is a fibrous zeolite mineral composed of alkaline alumino-silicate hydrate, which occurs naturally in admixtures with other zeolites in rocks. The general population is thought to be exposed incidentally in the environment. Synthetic zeolites are not considered in this volume.

Mechanisms of biological activity

The fate of inhaled particles (fibrous and nonfibrous) is dependent on factors such as morphology, aerodynamic size, surface properties, chemistry, durability and cytotoxicity.

Dust particles of appropriate size are rapidly taken up by macrophages, but this reaction occurs much less readily with longer fibres. Macrophages are activated by the process of phagocytosis and produce a large number of biologically active substances, which have many functions, including recruitment of additional macrophages and other inflammatory cells, direct stimulation of fibroblasts and stimulation of the immune response. The role of these factors in carcinogenesis is still uncertain. Evidence from studies of humans and experimental animals points to an association between pulmonary fibrosis and lung cancer following exposure to certain dusts.

Hypotheses about the mechanisms by which dusts cause cancer include the genetic effects of particles, the presence of other carcinogens carried by the dusts, the possible role of the inflammatory reaction in stimulating epithelial proliferation and the role of scar tissue.

With regard to fibrous particles, morphology appears to be especially important, since fibre length and diameter appear to be critical factors for carcinogenicity. Chemistry and physicochemistry also appear to be involved.

Complexity of exposures to mineral dusts

Minerals rarely occur in a pure form in nature, nor are they physically invariant, nor do they commonly occur alone as isolated, single phases. They often have substituted elements within their structures and occur in a range of forms and morphological habits and with other minerals. Such variations affect the biological activity of minerals and powdered admixtures. For example:

- Silica polymorphs, including quartz and its varieties, can contain trace impurities, which are thought to reduce the biological activity of 'free silica'.
- Wollastonite, derived by metamorphism of dolomite rocks, can not only vary chemically but can also occur geologically with fibrous amphiboles.
- Attapulgite and sepiolite clays vary considerably with regard to chemistry, crystal form, fibre length and the presence of associated, admixed gangue minerals.
- Talc can occur as plates or fibres, can contain substantial concentrations of metals and can be contaminated by serpentine minerals (including chrysotile asbestos), amphiboles (asbestiform and nonasbestiform) and free silica in the form of quartz.
- Erionite varies in fibrosity and generally occurs naturally in association with other zeolite minerals, one of which, mordenite, may also be fibrous.

Occupational exposures to mineral dust are therefore particularly complex. A mineral mixture to which workers are exposed may differ according to geological source. Workers in different processes, such as mining, milling, production and use, may be exposed to different mineral phases, especially if extensive beneficiation is employed; or they may be exposed to single minerals with very different properties, such as particle size, surface properties and crystallinity, due to alterations during industrial processing. Workers are additionally exposed to other agents in the occupational environment.

GENERAL REMARKS

35

Epidemiological methodology in estimation of human carcinogenicity

Problems of cancer epidemiology include the fact that disease latencies are seldom less than 20 years; there is often a paucity of biological or environmental measurements of exposure; levels of risk are usually such that they necessitate large denominators; and there often exist potent social, occupational and personal confounders. These difficulties were all encountered when reviewing epidemiological data for the six materials covered in this volume. The industrial exploitation of wollastonite, attapulgite and sepiolite is relatively recent — only within this century — and the total numbers of persons with well-defined exposure are small. There has been little commercial production of erionite; the few, small exposed communities in rural Anatolia present special investigative problems. Exposures to talc and silica are almost universal and almost always complicated by the presence of a variety of other known or potential carcinogens.

The epidemiological approach is deceptively simple; even advanced texts do not sufficiently convey the magnitude of the pitfalls that await the unwary. Epidemiological surveys, although occasionally experimental, are overwhelmingly observational. They are thus susceptible to bias in selection of study subjects and groups, in choice of referents and in assessment of exposure in ascertainment and recording of outcome.

Apart from questions of study design, the weakest aspect of the epidemiological studies reviewed in this volume is the qualitative and quantitative assessment of exposure. Deficiencies in environmental data of 20-50 years ago cannot now be rectified. The development of increasingly reliable and more easily interpretable measures of body burden, and other more sophisticated exposure indicators, should result in the future in better estimates of past exposures.

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THE MONOGRAPHS

SILICA

1. Chemical and Physical Data

1.1 Synonyms and trade names

CAS Registry No.: 7631-86-9

Chem. Abstr. Name: Silica

Synonyms^a: Amorphous: colloidal silica; diatomaceous earth; diatomite; fumed silica; fused silica; kieselguhr; opal; precipitated silica; silica gel; silica glass; silica soot; vitreous silica

Crystalline: chalcedony; chert; coesite; cristobalite; cryptocrystalline silica; flint; jasper; microcrystalline silica; novaculite; quartz; quartzite; sandstone; silica sand; stishovite; tridymite; tripoli

Trade names^a: Amorphous: Aerosil; Cab-O-Sil; Celite; Ludox; Silcron G-910

Crystalline: BRGM; D & D; DQ12; Min-U-Sil; Sil-Co-Sil; Snowit

The term 'silica' is used to refer to naturally occurring materials composed principally of silicon dioxide (SiO_2). The overwhelming majority of natural crystalline SiO_2 exists as quartz (CAS No. 14808-60-7).

1.2 Structure of typical minerals

Molecular formula: SiO_2

The basic structural units of the silica minerals are silicon tetrahedra, SiO_4 . These are linked by sharing each of their four corners with another tetrahedron to form a three-dimensional framework (Deer *et al.*, 1966). Slight variations in the orientation of the silicon tetrahedra with respect to each other result in the development of new symmetry, producing the different crystalline polymorphs of silica; a completely random orientation of these units results in the amorphous varieties of the material. Differences in symmetry and cell parameters are designated by the prefixes α - and β -.

The structures of the crystalline forms of silica have been studied extensively, and the symmetry and cell parameters (a, b, c: unit cell dimensions) of these forms are given in Table 1.

^aOnly common forms and those materials used in studies described in the monograph are included.

The structure of quartz is more compact than that of either tridymite or cristobalite (Deer *et al.*, 1966) and this is reflected in the different specific gravities of these materials (see below).

Table 1. Symmetry and cell parameters of crystalline forms of silica^a

Form	System	Cell parameters (nm)		
		a	b	c
α -Quartz	Trigonal	0.491	—	0.541
β -Quartz	Hexagonal	0.501	—	0.547
α -Tridymite	Orthorhombic	0.988	1.71	1.63
β -Tridymite	Hexagonal	0.503	—	0.822
α -Cristobalite	Tetragonal	0.497	—	0.692
β -Cristobalite	Cubic	0.713	—	—
Coesite	Monoclinic	0.717	1.238	0.717
Stishovite ^b	Tetragonal	0.418	—	0.266

^aFrom Deer *et al.* (1967), except when noted

^bLanger (1978)

The amorphous varieties of natural silica are opaline in character (Langer, 1978) and are exogenic products formed from dissolved silicate minerals. They are described as hydrous cryptocrystalline or colloidal forms of silica. Amorphous forms often appear to display a layered structure, most marked in opal gemstones, but this is a result of the manner in which they formed, having been deposited as thin layers of colloidal silica. Very rarely, amorphous silica occurs naturally with a glassy structure (e.g., lechatelierite).

1.3 Chemical and physical properties of selected silica forms^a

Property	α -Quartz	α -Cristobalite	α -Tridymite
Hardness (Mohs' scale)	7	6.5	7
Density	2.65	2.33	2.26
Cleavage	Poor	Poor	Poor
Twining	(1) Twin plane (10 $\bar{1}$ 1)r (2) Twin plane (01 $\bar{1}$ 1)z (3) Twin plane (10 $\bar{1}$ 0)m	Spinel-type twins on (111)	Common on (110)
Colour	Colourless, white or variable, black, purple, green	Colourless, white or yellowish	Colourless or white
Description	Occurs as hexagonal crystals; more commonly naturally in an anhedral massive form	Occurs as octahedral, rarely cubical, crystals; also in massive form	Occurs as tabular, pseudohexagonal crystals; also in massive form

^aFrom Deer *et al.* (1966) and Roberts *et al.* (1974)

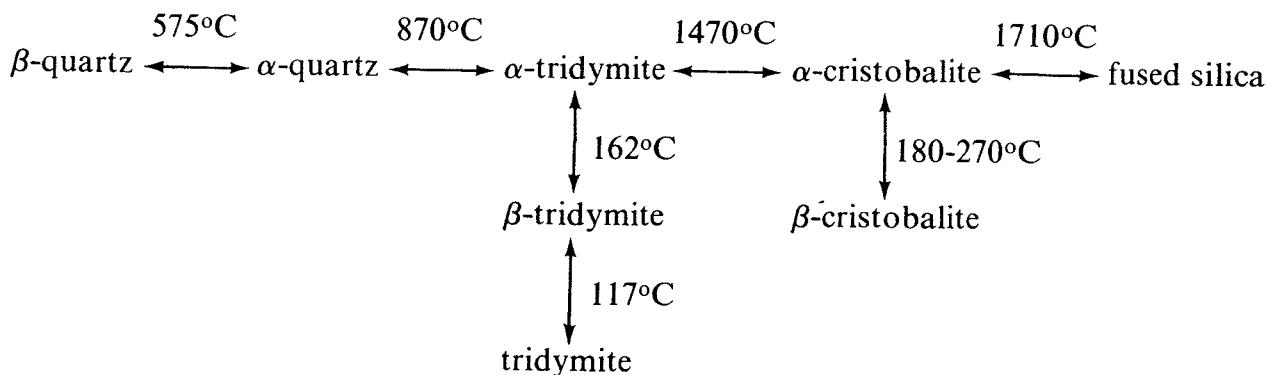
SILICA

41

Diatomite is a loosely coherent, chalk-like sediment from unicellular algae, which contains up to 94% SiO₂. The powder packs so loosely that its apparent density may be as low as 0.62. The hardness of individual particles is 4.5-5 (Harben & Bates, 1984).

Quartz, cristobalite and tridymite are interrelated and may change their form under different conditions of temperature and pressure (Deer *et al.*, 1966). The α , or low-temperature, forms are most common.

Approximate temperatures at which the various forms of silica interchange are as follows (Zaidi, 1969):



1.4 Technical products and impurities

Silica sand, sand and gravel, sandstone and quartzite

Silica (or industrial) sand deposits are high in silica content, although impurities may be present at up to 25%. More typically, silica sand contains more than 95% silica and minor amounts of free minerals. The chemical composition of several North American commercial products is presented in Table 2. Silica sand products are marketed in a wide range of grades, including extremely fine grades known as 'flours'.

Table 2. Chemical compositions of one silica sand, three sandstone and two quartzite samples, from Canada and the USA

Component	%
SiO ₂	96.71-99.83
Al ₂ O ₃	0.05- 1.71
Fe ₂ O ₃	0.02- 0.17
TiO ₂	≤ 0.06
CaO	≤ 0.08
MgO	≤ 0.05
Na ₂ O + K ₂ O	≤ 0.34
Fusion loss	≤ 0.35

^aFrom Murphy and Henderson (1983)

One high-purity, small-particle α -quartz sandstone with the trade name Min-U-Sil 15 was found to contain 99% α -quartz and traces of feldspar (Nolan *et al.*, 1981). The particle size of Min-U-Sil 5 was found to be distributed as follows: 0.1%, $> 5 \mu\text{m}$; 7%, 2–4.9 μm ; and 92.8%, $< 1.9 \mu\text{m}$ (Groth *et al.*, 1986).

Diatomite

Commercial diatomite deposits differ markedly in silica content, although most contain between 86–94% silicon dioxide. Since diatomite is a sedimentary rock, other sediments, especially clays, may be associated with the ore. Table 3 summarizes the chemical compositions of ten diatomite ores from seven countries (Kadey, 1975).

Commercial diatomite products are marketed in many grades, almost exclusively as fine powders. Diatomite for filtering is typically calcined or flux-calcined using a soda ash or sodium chloride flux. The heat of calcination often causes conversion of amorphous silica to cristobalite (Kadey, 1975). Cristobalite and, to a much lesser extent, tridymite occur in association with high-temperature products such as calcined diatomite (Deer *et al.*, 1966).

Other forms of amorphous silica

Amorphous silica exists in a variety of synthetic forms including colloidal silica, silica gels, precipitated silica and fumed silica (Willey, 1982).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(a) *Production*

Naturally occurring silica materials have so many applications that they are often classified by end use or industry. For instance, ‘sand and gravel’, a commodity group including various silica containing materials, is produced almost exclusively for road building and concrete construction. According to Goldman and Reining (1975), the definition of sand and gravel is based solely on use criteria, which include such characteristics as particle size and shape, surface texture and abundance of natural pores. Nevertheless, highly pure silica sand, which may be extracted from a sand and gravel operation, is also a major industrial commodity. Similarly, products marketed as ‘quartz’ and ‘quartzite’ are also of high purity. Here, only the production of silica sand, quartz and diatomite are discussed.

Silica sand

Silica-bearing deposits are found to some degree in every land mass and strata from every era and period of geological time. Silica deposits are almost uniformly quartz or derived from quartz, formed by metamorphism, sedimentation or through igneous activity. The majority of deposits mined for silica sand consist of free quartz, quartzites and quartzose sedimentary deposits, such as sandstone (Murphy & Henderson, 1983; Harben & Bates, 1984).

Table 3. Composite chemical composition (%) of ten diatomite ores (oven-dried basis)^a

Component	Lompoc, CA, USA	Maryland, USA Calvert formation	Nevada, USA	Idaho, USA	Kenya, Soysambu	Japan, Nilgata earth	USSR, Kamyshlov, Urals	Spain, Albacete	Mexico, Jalisco	Algeria (primo grade)
SiO ₂	89.70	79.55	86.00	89.82	84.50	86.0	79.92	88.60	91.20	58.40
Al ₂ O ₃	3.72	8.18	5.27	1.82	3.06	5.8	6.58	0.62	3.20	1.66
Fe ₂ O ₃	1.09	2.62	2.12	0.44	1.86	1.6	3.56	0.20	0.70	1.55
TiO ₂	0.10	0.70	0.21	0.07	0.17	0.22	0.48	0.05	0.16	0.10
P ₂ O ₅	0.10	—	0.06	0.13	0.04	0.03	—	—	0.05	0.20
CaO	0.30	0.25	0.34	1.26	1.80	0.70	1.43	3.00	0.19	13.80
MgO	0.55	1.30	0.39	0.54	0.39	0.29	0.98	0.81	0.42	4.57
Na ₂ O	0.31 {	1.31	0.24	1.03	1.19	0.48	0.65	0.50	0.13	0.96
K ₂ O	0.41 {		0.29	0.22	0.91	0.53	0.72	0.39	0.24	0.50
Ignition loss	3.70	5.80	4.90	4.02	6.08	4.4	4.91	5.20	3.60	17.48 ^b

^aFrom Kadey (1975)^bIncludes 13.9% CO₂

SILICA

Silica sand was probably first collected for making glass over 4000 years ago. It is still mined mainly in open-quarry operations, but some underground mining is carried out to obtain access to deposits with an unusual amount of overburden. Processing operations depend on the nature of the deposit and the desired end product but generally include initial crushing, secondary milling to refine particle size and, if necessary, wet or dry screening to create very fine particles (Davis & Tepordei, 1985).

World production of silica sand has been relatively stable for the last 10-15 years. Davis and Tepordei (1985) estimated world production at 182 million tonnes in 1983. Estimates of production by world region and country are presented in Table 4.

Table 4. Silica sand production 1983 and estimated capacity 1983 and 1984^a

Region/Country	Production (1983)	Capacity (10 ⁶ tonnes)	
		1983	1984
Africa	23.6	29.1	29.1
Asia	40.8	45.4	45.4
Australia	1.8	2.7	2.7
Europe			
Belgium	2.3	4.5	4.5
France	5.5	7.3	7.3
Germany, Federal Republic of	5.5	8.2	8.2
Spain	1.8	2.7	2.7
United Kingdom	4.1	6.4	6.4
Yugoslavia	2.3	2.7	2.7
Other	32	41	41
North America			
Canada	1.6	2.7	2.7
Mexico	1.8	2.3	2.3
USA	23.7	31.8	31.8
South America			
Argentina	0.9	2.3	2.3
Brazil	4.1	7.2	7.2
Other	27.3	36.3	36.3

^aFrom Davis and Tepordei (1985)

The largest producer, the USA, currently exports only a small fraction (4%) of its domestic supplies (Davis & Tepordei, 1985), principally to Canada and Mexico (Anon., 1976a), and does not import significant quantities. Many European producers, notably Belgium, France, the Netherlands and the Federal Republic of Germany, both import and export large amounts, almost exclusively within Europe. Italy is the largest importer of silica sand in Europe (Anon., 1984).

Quartz crystals

Quartz was probably first used as a gem stone several thousand years ago. When the applications of pure quartz in the electronics industry were discovered, large quantities of pure crystals were required. Today, the demand for this grade comes from both electronics and optical components industries (Smith, 1984a).

The largest reserves of highly pure quartz occur in Brazil in sedimentary strata containing sandstone and quartzite rocks. Minor deposits have been tapped in the USA, Angola, India and Madagascar. Mining procedures are known to be primitive, and most quartz crystal is extracted with hand tools in small open pits (Harben & Bates, 1984; Smith, 1984a,b).

The leading producer and exporter of high-purity quartz is Brazil. Since reported production statistics include all forms of quartz, it is difficult to estimate the amount of high-grade material mined. Total exports of quartz in 1983 were 8782 tonnes, mainly in the form of 'lascas', the precursor material for cultured (synthetic) quartz crystals. In 1981-1983, most exports went to Europe, Japan and the USA (Smith, 1984a,b).

Most of the high-purity quartz mined industrially in the USA is in the form of lascas. Recently reported US production figures are given in Table 5. Much of US production is exported to western Europe and Japan.

Table 5. US production of high-purity quartz (lasca only)^a

Year	Production (tonnes)
1979	143
1980	182
1981	79
1982	90
1983	363

^aFrom Smith (1984a)

India exports small quantities, mainly to Japan (Smith, 1984a).

Diatomite

Diatomite, or diatomaceous earth, is a rock formed by the sedimentation of microscopic plants called diatoms over the tertiary and later periods. Diatomite may be characterized as opaline hydrous silica, the concentration of which may vary in commercial deposits from 86 to 94%. Associated materials are generally clay minerals (Kadey, 1975; Dickson, 1979; Harben & Bates, 1984).

The most notable commercial source of diatomite is in California, USA, where there is a marine deposit of unusual purity over 300 m thick. Other major mineable deposits occur in France, Denmark, Romania, Algeria and Iceland (Dickson, 1979; Reimarsen, 1981; Harben & Bates, 1984).

Diatomite is mined almost exclusively by open-pit methods, using bulldozers and similar equipment to remove the material. Some diatomite is mined underground in Europe, Africa, South America and Asia. In one operation in Iceland, the slurried mineral, which lies under one metre of water, is dredged and transferred to a processing plant by pipeline (Kadey, 1975).

The rock must be processed because of its naturally high moisture content, which is typically over 60%. After initial crushing, the aggregates are milled while being dried simultaneously with hot air. Cyclone separators are used to eliminate impurities, after which the material is sorted and bagged (Kadey, 1975).

The USA has dominated the world diatomite market for many years, contributing up to 35% of world production. Denmark and France are the next largest producers, accounting for another 25%, with the remaining amount divided among many European, African and Asian countries (Dickson, 1979). Diatomite production by region during the years 1950-1983 is presented in Table 6.

Table 6. World diatomite production, 1950-1983, by region or country^a

Region/Country	Major producers	Production (thousands of tonnes)				
		1950	1960	1970	1980	1983
Europe	Denmark, France, Iceland, USSR	170	404	778	733	740
North America	USA	244	434	578	686	621
Asia	Republic of Korea	0.1	9	8	27	56
South America	Brazil	0.1	3	11	31	21
Africa	Algeria	17	26	12	7	7
Australia		6	5.4	3	3.6	1.8

^aFrom Colonial Geological Surveys (1957); Institute of Geological Sciences (1967, 1978); British Geological Survey (1985)

The USA and Denmark are the major world exporters of diatomite. The USA exported almost 25% of its 1983 production to Europe, Canada, Japan and Australia (Dickson, 1979; British Geological Survey, 1985). Canada and the Federal Republic of Germany are large net importers (British Geological Survey, 1985).

(b) Use

Silica sand

Although silica sand has been used for many different purposes for many years, its principal use throughout history has been in the manufacture of glass (Davis & Tepordei, 1985). Sand with a silica content greater than 98.5% and a low iron content is used as an ingredient in the manufacture of both glass and ceramics (Anon., 1976b).

SILICA

47

The other major use of silica sand is in foundry castings. A grade usually lower in purity than that used for making glass is added to clay to form moulding mixtures for casting iron, aluminium and copper alloys. Another significant industrial application is incorporation into abrasives, such as sandpaper, grinding and polishing agents, and sandblasting materials (Anon., 1976b; Davis & Tepordei, 1985).

A major US use of silica sand in recent years is in hydraulic fracturing. Sand is suspended in a fluid and pumped into oil or gas wells to increase rock permeability and thereby increase recovery (Anon., 1976b). In 1983, approximately 850 000 tonnes of US silica sand were used in hydraulic fracturing (Davis & Tepordei, 1985).

Consumption of silica sand in the USA in 1973-1983 was relatively stable in all use categories, except in foundries, where consumption declined significantly from 1978 to 1983. Consumption in 1983 was as follows: glass sand, 37.4%; foundry sand, 26.7%; abrasives, 8%; hydraulic fracturing, 4%; and other uses, 23.9%. A similar predominance of use in glass and foundry industries has been observed in other regions, as shown by recent estimates of French (40% glass, 37% foundry) and British use (47% foundry, 41% glass) (Anon., 1984).

Silica sand is also used industrially in several other ways of lesser importance. It is used as a raw material for the production of silicon and ferrosilicon metals, the abrasive silicon carbide, activated silica, silica gel desiccants and sodium silicate and as a builder in detergents (Anon., 1976b). Silica sand may also be used in filtering equipment for large-volume systems, such as municipal water and sewage-treatment systems. Silica bricks and tiles are commonly used for furnace linings and beds, coal washing and pottery kilns. Finely ground sand (silica flour) has been used as a filler in paints, rubber, paper, plastics, asphalt, scouring powders, cements and other products (Davis & Tepordei, 1985).

Quartz crystals

Pure quartz was used mainly for jewellery, until its dielectric and piezoelectric properties were discovered in about 1880. The latter property allows quartz crystals to be used in radio oscillator circuits to control electromagnetic wave frequencies. Electronic applications have created a demand for natural and synthetic quartz crystals of the highest purity. This material has also recently been used for special optical applications, such as fibre optics (Smith, 1984a).

The major consumers of natural and synthetic quartz are the USA and Japan, although the Republic of Korea, Taiwan, Singapore and Hong Kong are also major markets. Specific applications probably differ minimally among these countries, which use most natural and synthetic crystals in the manufacture of watches, microcomputers, television equipment and wireless communications equipment (Smith, 1984a).

Diatomite

The intricate microstructure and high pore-space volume of diatomite have made it a major substrate for filtering, and about half of the world's production is used in this way (Sinha, 1982). Diatomite has been used to filter or clarify dry-cleaning solvents, pharmaceuticals, beer, whisky, wine, municipal and industrial water, fruit and vegetable

juices, oils, fuels, coatings and other chemical preparations. Filtering aids are marketed for specific uses, so that particle size is normally matched to the characteristics of the material being filtered (Kadey, 1975).

The next most important application of diatomite is as a filler in paint, paper and scouring powders. It imparts natural abrasiveness to polishes, flow and colour qualities to paints, and reinforcement to paper. It is also used as a carrier for pesticides, a filler in synthetic rubber goods, in laboratory absorbents and in anticaking agents (Kadey, 1975; Sinha, 1982).

Diatomite is used mainly in filtering and filler applications and as an insulating agent throughout the world, although these uses are not necessarily representative for every country. The production of one diatomite facility in Northern Ireland is distributed as follows: 75% for incorporation into insulating bricks, 20% for insulating cements and 5% for use in fertilizers (Dickson, 1979).

(c) Regulatory status and guidelines

Occupational exposure limits in selected countries are listed in Table 7.

Table 7. Occupational exposure limits for respirable quartz, cristobalite, tridymite and amorphous silica (mg/m³)^a

Country (year)	Quartz	Cristobalite	Tridymite	Amorphous silica
Australia (1978)	0.25 ^b	0.25 ^b	0.25 ^b	
Belgium (1978)	0.10 ^c	0.05 ^c	0.05 ^c	
Bulgaria (1978)	0.07	0.07	0.07	
Czechoslovakia (1976)				
total dust below 10% free SiO ₂	5	5	5	
total dust 10-70% free SiO ₂	2	2	2	
total dust above 70% free SiO ₂	1	1	1	
Denmark (1984)	0.10	0.05	0.05	1.5
Finland (1981)	0.20	0.10	0.10	5 (total dust)
France (1986)	0.10 ^c	0.05 ^c	0.05 ^c	5
Germany, Federal Republic of (1986)	0.15	0.15	0.15	
Italy (1978)	0.10 ^c	0.05 ^c	0.05 ^c	1
The Netherlands (1982)	0.15	0.075	0.075	
Norway (1981)	0.20	0.10	0.10	2
Poland (1976)				
total dust below 10% free SiO ₂	4	4	4	
total dust 10-70% free SiO ₂	2	2	2	
total dust above 70% free SiO ₂	1	1	1	
Sweden (1984)	0.10	0.05	0.05	
Switzerland (1978)	0.15	0.15	0.15	10 (total dust)
UK (1985)	0.10 ^c	0.05 ^c	0.05 ^c	3

SILICA

49

Table 7. (contd)

Country (year)	Quartz	Cristobalite	Tridymite	Amorphous silica
USA				
ACGIH (1985)	0.10	0.05	0.05	10 (total dust)
OSHA (1983)	0.10 ^c	0.05 ^c	0.05 ^c	
MSHA (1977)	0.10 ^c	0.05 ^c	0.05 ^c	
NIOSH (1974)	0.05	0.05	0.05	
USSR (1976)				
total dust below 2% free silica	6	6	6	
total dust 2-10% free SiO ₂	4	4	4	
total dust 10-70% free SiO ₂	2	2	2	
total dust above 70% free SiO ₂	1	1	1	1 (total dust)
Yugoslavia (1971)	0.10 ^c	0.05 ^c	0.05 ^c	

^aFrom the National Institute for Occupational Safety and Health (NIOSH) (1974); Mine Safety and Health Administration (MSHA) (Banks *et al.*, 1981a); Työsuojeluhallitus (1981); Arbeidsinspectie (1982); Direktoratet for Arbeidstilsynet (1981); US Occupational Safety and Health Administration (OSHA) (1983); Arbetarskyddsstyrelsen (1984); International Labour Office (1984); American Conference of Governmental Industrial Hygienists (ACGIH) (1985); Health and Safety Executive (1985); NIOSH (1985); Deutsche Forschungsgemeinschaft (1986); Institut National de Recherche et de Sécurité (1986)

^bCalculated from the formula: 25 mg/m³/q+5, where q is the percentage of free silica in respirable dust

^cCalculated from the formula: 10 mg/m³/q+2, where q is the percentage of free quartz in respirable dust

2.2 Occurrence

(a) Natural occurrence

Feldspar and quartz are the most abundant minerals on the Earth's surface; quartz constitutes about 12% of continental land masses. Tridymite and cristobalite occur in a number of mineral deposits and can be formed by natural conversion of quartz or amorphous silica (Murphy & Henderson, 1983).

Some 25% of the Earth's surface is made up of crystalline rocks, of which the igneous type are the most common. The occurrence of silica-containing minerals in different rock types is shown in Table 8. Granites, coarse-grained igneous rocks, generally contain 25-30% quartz; the other major component is feldspar, and there is a wide range of minor constituents such as mica and garnet. About 75% of the Earth's dry surface is covered by a veneer of sedimentary rocks, most of which are shale, sandstone and limestone. Shales may contain up to 30% quartz; sandstone is predominantly quartz; limestones are primarily composed of carbonate minerals, but may contain substantial amounts of silica polymorphs. Diatomite is a sedimentary rock occurring throughout the world, which is composed principally of amorphous silica. The mineralogical composition of the metamorphic rocks tends to reflect the materials from which they are derived. Quartzite is a recrystallized product from sedimentary sandstone or siltstone. The principal types of clays, sands and gravels, determined by their origin, are stream, glacial, residual, marine, lake and

Table 8. Silica-containing minerals found in generic rock types^a

Rock type	Silica-containing minerals
Igneous	Quartz and other silica polymorphs Feldspars Micas Amphiboles Pyroxenes Olivines
Sedimentary	Quartz and other silica polymorphs Feldspars Micas Clays Carbonates
Metamorphic	Quartz and other silica polymorphs Feldspars Micas Amphiboles Epidotes Garnets Aluminium silicates

^aFrom Langer (1980)

windblown. Quartz is the major constituent of most commercial sands. In addition to the three basic rock types, accompanying gangue minerals in a number of metallic and nonmetallic ore bodies, as well as in fossil fuels, may contain quartz (Kadey, 1975; Langer, 1980; Murphy & Henderson, 1983; Rogers *et al.*, 1983; Davis & Tepordei, 1985).

(b) Occupational exposures

Potential occupational exposures to crystalline silica are widespread; the US National Institute for Occupational Safety and Health (1983) estimated that approximately 3.2 million workers in 238 000 plants in the USA were potentially exposed to crystalline silica. Silica exposures occur during mining and quarrying of coal and other minerals (metals and nonmetals), during stone cutting and construction, during production of glass and ceramics, in foundries and in various other occupations such as sandblasting, polishing and grinding.

Throughout this section, the term 'silica' is used to mean unbound or 'free silica' (quartz). Until approximately 1970, the sampling method most commonly used to evaluate occupational silica exposures was counting of particles by optical microscopy; the quartz content of the airborne dust was inferred from analyses of product and settled dust samples. The method currently used by most occupational hygienists is sampling of the respirable mass combined with analysis for silica. In eastern European countries, standard procedures involve the use of stationary samples, and results are usually reported as total dust concentrations, supplemented by data on silica content. This section contains summaries of

studies in which information based on gravimetric measurements of silica exposures is presented, and studies are grouped according to the method of measurement.

Ore mining and quarrying

Silica exposures occur in nearly all metal and nonmetal mining and milling operations, as well as during mineral processing. Chen *et al.* (1983) analysed respirable dust samples collected by the US Mine Safety and Health Administration in metal and nonmetal mines between 1977 and 1981. More than 45 000 respirable dust samples containing silica (quartz, cristobalite or tridymite) were available for analysis. Geometric mean respirable silica exposures were below 0.05 mg/m³ in most of the 15 industry and 14 operation categories included in the survey; but in 64% of the categories at least 5% of airborne samples contained more than 0.10 mg/m³. Among the mining industries analysed, in those for copper, gold and silver, molybdenum, iron, uranium, lead and zinc, stone, clay and shale, sand and gravel, and other nonmetal industries, several operations involved respirable silica concentrations of greater than 0.05 mg/m³. Of all the samples analysed, only 175 (<0.4%) were reported to contain cristobalite or tridymite in concentrations greater than 1%.

Watts *et al.* (1984) also analysed respirable silica exposures in metal and nonmetal mines in the USA; their analysis included 41 502 respirable silica samples taken in 1974-1981. Workers in sandstone, clay and shale, and miscellaneous nonmetallic mineral mills had the highest exposures to silica dust: 2.2-40.9% of the samples exceeded the applicable exposure limit [calculated from the formula: 10 mg/m³/(% SiO₂ + 2)]. Within the mills, the occupations in which there were the highest exposures were baggers, general labourers and persons involved in crushing, grinding and sizing operations. Cristobalite was found in 168 samples and tridymite in three. The authors noted that other agents most frequently sampled in US metal and nonmetal mines included noise, methane, carbon monoxide, radon daughters, carbon dioxide, oxygen, nuisance dusts, nitrogen dioxide and hydrogen sulphide. Workers in metal and nonmetal mines are also potentially exposed to fibrous minerals and trace metals.

Workers in mills producing silica flour, by grinding and milling quartz or quartzite rock, are also exposed to high levels of silica dust. Nelson *et al.* (1978) showed that over 98% by weight of the particles in silica flour products are <5 µm in size. They measured silica exposures in four mills in Ontario, Canada, and found average respirable dust concentrations ranging from 0.21 to 0.55 mg/m³, with a high quartz content. Banks *et al.* (1981b) investigated silica exposures in two US silica flour mills where advanced cases of silicosis had been observed among plant employees: 77 (85%) of 91 personal samples of respirable dust collected at the two mills contained more than 0.05 mg/m³ dust made up of 95-98% crystalline silica. Cleaning personnel and bagging machine operators were exposed to average respirable concentrations of 0.65 and 1.0 mg/m³, respectively (13 and 20 times the recommended limit). Banks *et al.* (1981a) reviewed data from inspections carried out by the Mine Safety and Health Administration in 27 US silica flour mills from 1974-1979. Of the 1044 dust samples reported, 563 (54%) contained more than 0.10 mg/m³ respirable silica (the MSHA standard, see Table 7).

In Swedish mining and quarrying industries, total dust exposures averaged 4.5-8.4 mg/m³, of which the quartz content ranged from 7% in metal-ore mines to 46% in quartzite quarries (Gerhardsson *et al.*, 1974). In Norwegian mines, total dust levels ranged from 0.5 to 36 mg/m³ (23-32% silica in the respirable fraction) in an iron-ore mine (in which miners were also exposed to cummingtonite-grunerite fibres; Gylseth *et al.*, 1981) and from 17 to 57 mg/m³ (4.0-7.7% silica in the respirable fraction) in a graphite mine (Hanoa, 1985). In six Italian metal mines, respirable dust concentrations were 0.7-1.7 mg/m³, with a mean quartz content of 2.8-4.0%, for several underground and surface occupations (Casula *et al.*, 1983). In 135 UK quarries producing gravel, sand, clay, limestone and other nonmetal materials, the median concentration of respirable dust in 285 samples was 6 mg/m³; the quartz content was <10% in 99 samples, 11-30% in 143 samples and >30% in 43 samples (Maguire *et al.*, 1975).

In six Rhodesian copper mines, the quartz content in the respirable fraction of dust averaged 19-43% (Paul, 1961). Mean data for several South African gold mines were: 0.7 mg/m³ total dust, 0.5 mg/m³ respirable dust, 31% quartz in the respirable fraction, and 0.2 mg/m³ respirable quartz in the air (Beadle & Bradley, 1970).

The quartz content of airborne dust in 14 iron-ore fields in the USSR varied from 20 to 42%, although in one mining area it was reported to be as low as 3.9% (Gagaous, 1984). The quartz content of total dust was 25-30% in gold mines and 1-45% in copper fields. During the period 1956-1962, mean concentrations of total dust in drilling and other operations in ore mines in Kazakhstan decreased steadily from about 13 mg/m³ to 2 mg/m³, due to the application of control measures. In lead-zinc and tungsten mines in Tadzhikistan, total dust concentrations were 0.6-4 mg/m³. As reported in 1959, of 13 500 measurements made during a five-year period in three copper mines, 23% showed less than 2 mg/m³ and 70% of them 2-10 mg/m³. Since the 1960s, average total dust concentrations in metal mines were less than 2 mg/m³; levels below 1 mg/m³ were found in mines in which dust control measures had been strictly observed, but concentrations of up to 30 mg/m³ were reported in mines where dust control was neglected (Huhrina & Tkachev, 1968a).

Total dust concentrations higher than the maximum acceptable concentration (2 mg/m³) were measured in underground mining of ores containing beryllium in the far north of the USSR. The content of free crystalline silica in the dust ranged from 27 to 54%, with a mean of 39% (Lutai *et al.*, 1979).

Total dust concentrations varied from 1.3 to 24.9 mg/m³ in the cabs of drilling machines and from 0.8 to 4.8 mg/m³ in the excavator cabs during various stripping and mining operations in open-cast mining of chromium ore in the USSR. The highest concentrations were measured during manual drilling of stone lumps, with a mean of 46 mg/m³ and a maximum of 93 mg/m³. In a screening plant, dust concentrations ranged from 10 to 188 mg/m³. The percentage of free crystalline silica in total dust was 6-16% at different places in the mine and 3-10.7% in the dressing plant. The chromic oxide content in mine dust did not usually exceed 3.9%, and in the dressing plant it ranged from 30 to 45%. No hexavalent chromium was found in the dust (Pokrovskaja *et al.*, 1976).

Dust measurements were also performed at an open-cast mine at the Kursk magnetite deposit in the USSR. Workplace dust concentrations ranged from 7.0 to 91 mg/m³ in one

SILICA

53

conveyor system and from 1.6 to 2.6 mg/m³ in another (Neplokhov, 1979). During various mining operations in Zabajkal'sk, mean concentrations of respirable dust, measured with a gravimetric sampler SPG-10, were 0.2-1.6 mg/m³, with a free crystalline silica content of 9.6-17.3% (Table 9). The respirable fraction was 33-35% at low concentrations of total dust (0.6-3.1 mg/m³) and below 12% at 13.7 mg/m³ total dust (Duve & Tkachev, 1982).

Table 9. Workplace concentrations of total and respirable dust (mg/m³) and of free crystalline silica (%) in an ore mine in Zabajkal'sk, USSR^a

Process	No. of samples	Dust concentration (mg/m ³)		Free crystalline silica (%)	
		Total	Respirable	In total dust	In respirable dust
Drilling	—	13.7	1.6	—	—
Clearing	22	2.4	0.9	30.6	15.0
Driving	19	3.1	1.1	16.3	9.6
Power loading and unloading	11	0.6	0.2	27.2	17.3

^aFrom Duve and Tkachev (1982)

In the production of pellets from magnetite concentrate and bentonite, total dust concentrations averaged 3.4-8.1 mg/m³ in some work places of a plant in the USSR. In the 198 samples, the highest concentration was 49 mg/m³; the quartz content in the dust ranged from 2.7 to 3.4% (Kornilov, 1980). Dust concentrations of 47-117 mg/m³ were reported in the charging sections of two iron-ore processing plants in Krivoj Rog, USSR. The free crystalline silica content in the dust was 7-9%. Dust concentrations exceeded 20 mg/m³ during ore crushing, and were over 12 mg/m³ during pelletizing (Makarenko *et al.*, 1985).

In a study carried out in two gold mining and processing plants in the USSR, total dust concentrations of 0.7-17.2 mg/m³ were reported. Low concentrations (0.2-2.0 mg/m³) found in the storage and grinding departments of one plant were explained by the high moisture content of the processed ore, by the use of new equipment and by regular damp-cleaning of the premises. In contrast, the dust levels in the other crushing plant were 2.2-17.2 mg/m³. The quartz content of the airborne dust was 22-46% (Chebotarev *et al.*, 1979).

In underground mining of bauxite ore with low concentrations of silica (3-5%) in the northern Ural Mountains, total dust concentrations of 0.8-12.0 mg/m³ were measured during drilling and scraping operations and 0.6-6.3 mg/m³ when mechanized mining methods were used (Suhanova *et al.*, 1976).

During the mining of mica in the USSR, total dust concentrations of less than 10 mg/m³ were measured after dust controls were introduced. The quartz content of the dust varied from 25 to 30% (Huhrina & Tkachev, 1968b). Miners in the Kursk phosphorite fields were exposed to dust containing 10.1-17.8% free crystalline silica, whereas at mineral processing

sites, concentrations were of the order of hundreds of mg/m³. When the moisture in the phosphorite powder was increased from 2 to 4.8%, dust levels fell abruptly by 50 fold (Huhrina & Tkachev, 1968c).

During mechanized processing of volcanic tuffs in the Armenian SSR, Dashtoian *et al.* (1980) found mean dust concentrations that fluctuated widely, from 1.2 to 189 mg/m³. At most work places, mean total dust concentrations were between 10 and 100 mg/m³. [The authors gave no data on the free crystalline silica content of the dust.] According to Dashtoian (1976), the tuffs in Armenia contain 62-66% total silica and 1-2% quartz and cristobalite.

Spiridonova *et al.* (1982) reported that workers engaged in underground mining of limestone in the USSR were exposed to dust concentrations greater than 100 mg/m³. The free silica content of the dust varied from 0.5 to 6.0%.

During mining and processing of bentonite in the USSR, mean total dust concentrations in 220 samples were found to vary from 4.6 to 749 mg/m³. The free silica content of bentonite was low (0.1-0.9%). Structural and petrographic analyses of the bentonite showed that it consisted mainly of montmorillonite but also contained some cristobalite (Melkonian *et al.*, 1981).

During the mining of superficial deposits of ore minerals in the far north of the USSR, workers were exposed to mean total dust concentrations of 47-196 mg/m³. Lower concentrations (12-13 mg/m³) were measured in the mine yard and at the place of work of scraper operators (Lestenko *et al.*, 1981). In drilling and scraping operations, the concentration of total dust was 11-14 mg/m³ (22-27% quartz), and the level of respirable dust was 1.6-2.0 mg/m³ (12-13% quartz) (Duve & Tkachev, 1982).

In 1969-1980, in various Bulgarian underground ore mines, mean concentrations of total dust varied from 1.3 to 7.3 mg/m³, those of respirable dust from 0.36 to 1.60 mg/m³ and those of respirable quartz from 0.04 to 0.36 mg/m³. The quartz content of the respirable dust was 4-38%. When dust control was not completely effective, higher average concentrations were measured: 10 mg/m³ for total dust and up to 2.5 mg/m³ for respirable dust (Burilkov *et al.*, 1983a). The concentration of oil aerosols at pneumatic drilling sites varied from 1.2-21.1 mg/m³ (Dobreva & Lalova, 1967).

Average total and respirable dust concentrations and free crystalline silica contents in nonmetallic mining and processing plants in Bulgaria are shown in Table 10 (Burilkov *et al.*, 1983b).

During the mining and dressing of a zeolite (clinoptilolite) in Bulgaria, workers were exposed to dust containing 2% quartz and 10-12% cristobalite (poorly crystallized) in the fine fraction. Concentrations fluctuated widely, from 8.5 to 134 mg/m³ for total dust and from 7.7 to 17.3 mg/m³ for respirable dust. High concentrations were measured in dressing operations, but at mining sites the levels were low (Nikolova *et al.*, 1981).

Coal mining

In 1984, the US Mine Safety and Health Administration identified approximately 2400 work sites at which the level of 5% silica had been exceeded, representing the work

SILICA

55

Table 10. Mean concentrations of total and respirable dust (mg/m³) and free crystalline silica (%) during mining and dressing of nonmetallic minerals in Bulgaria, 1980-1985^a

Material and process	Concentration (mg/m ³)		Free crystalline silica content (%)	
	Total dust	Respirable dust	Total dust	Respirable dust
Asbestos-anthophyllite				
Underground mining	3.1-5.8	—	23.0	—
Open mining	44.6	—	—	—
Processing	59.0	—	4.3	—
Fluorite				
Underground mining	3.8-3.9	—	24.4-30.0	—
Mica				
Underground mining	6.4-7.7	—	10.2-10.8	—
Feldspar				
Open-cast mining	10.4-477	—	9.8-40.0	—
Processing	27.4-29.8	1.7	11.0-12.3	7.7
Clay				
Open-cast mining	2.8-4.2	—	—	—
Kaolin				
Underground mining	5.7	—	26.0	—
Processing	49.8-119	0.3	14.9-24.3	7.9
Perlite				
Open-cast mining	177	—	13.5	—
Processing	16.6-129	3.3	10.0-13.0	5.0
Bentonite				
Open-cast mining	1.3	—	2.0	—
Processing	16.3-244	3.4	2.0-3.7	2.9
Talc				
Processing	10.6	0.7	1.9	4.8
Tuff				
Processing	10.0	0.5	1.5	1.3
Chalk				
Processing	12.3	0.7	1.9	0.6
Talc-magnesite				
Processing	50.0	1.5	7.6	5.0
Quartz sand				
Processing	17.8-64.6	2.9	45.7-25.0	16.6
Barite				
Processing	4.1	—	8.2	—
Marble				
Processing	7.7	—	2.0	—
Andesite				
Drilling	294	43.3	13	13.9
Coarse crushing	40.0-144	1.9-4.5	11.3	10.4-11.6
Control board	1.7	0.5	—	5.0

Table 10 (contd)

Material and process	Concentration (mg/m ³)		Free crystalline silica content (%)	
	Total dust	Respirable dust	Total dust	Respirable dust
Dolomite				
Drilling	581	44.7	4.1	3.4
Loading	31.6	0.7	—	3.5
Screening	209	19.1	—	2.4
Crushing	3.4	0.5	—	2.2
Loading	2.7	0.5	—	2.9

^aFrom Burilkov *et al.* (1983b) and recent surveys performed by the Hygienic and Epidemiological Inspectorate, Bulgaria (Dobreva, 1986)

environment of 15 000-20 000 coalminers (approximately 10% of the US coal-mine work force). Major sources of exposure to silica in these mines were continuous mining machines, cutting of roof, floor and inclusion rock bands, and roof bolting operations. Floor and roof samples were found to contain 18-82% quartz, whereas coal itself contained only 1-4% (Jankowski *et al.*, 1984).

In the UK in 1970-1975, the mean return air concentration of respirable dust at eight out of 274 collieries was 3.6-11.5 mg/m³, and the mean quartz content in the respirable fraction varied from 1.5 to 10.3% (Crawford *et al.*, 1982). In a study of 20 collieries, mean exposures to respirable dust, with a quartz content of 0.8-7.8%, ranged from 1.2 to 8.2 mg/m³. Underground samples contained 12-77 mg/m³ total dust and 1.5-5.5 mg/m³ respirable dust; in face samples, the levels were 22-83 mg/m³ and 3.3-8.2 mg/m³, respectively. On average, coalface dusts contained 4.5% quartz, 10.8% kaolin and 8.2% mica (Dodgson *et al.*, 1971; Walton *et al.*, 1977).

Similar values for the mean quartz content of respirable dust were found in Belgium (4.2-14%) (Houbrechts, 1960), the Federal Republic of Germany (0.8-9.3%) (Reisner & Robock, 1977) and Spain (8.6%) (Gonzalez *et al.*, 1982). Mean data from coal fields in the Federal Republic of Germany are shown in Table 11.

In some South African coal mines, the quartz content was 2-3%; the estimated total dust levels during drilling, cutting, loading and surface work ranged from 3.9 to 12.5 mg/m³ (Goldstein & Webster, 1972).

The free crystalline silica content of coal dusts in some of the largest coal fields in the USSR are shown in Table 12. In 1965, total dust concentrations of 60-70 mg/m³ were measured during mechanized mining in the Kuzneck coal field and levels as low as 10 mg/m³ in some mines of the Doneck coal field (Huhrina & Tkachev, 1968d). During underground mining in the Kuzneck coal field, the quartz content was up to 3% in dust and up to 32% in rock (Balychev, 1981; Tolchenkin *et al.*, 1981). The highest mean concentrations of total dust at a deep shaft in the Doneck coal field were measured in driving (drilling) work (130 mg/m³) and the lowest (22 mg/m³) in support work. Workers were also exposed to

SILICA

57

Table 11. Dust concentrations in return air of coal mines in the Ruhr district of the Federal Republic of Germany^a

Stratum and survey period	Total dust concentration (mg/m ³)	Quartz content in respirable dust (%)	Respirable quartz concentration (mg/m ³)
Dorsten, Horst, Essen			
1955	7	3.3	0.23
1963-1967	5.6	3.7	0.21
Bochum			
1955	17	2.2	0.37
1963-1967	10.1	2.1	0.21
Witten, Sprockhövel			
1955	23	1.5	0.35
1963-1967	11.8	1.9	0.22

^aFrom Reisner *et al.* (1982)**Table 12. Free crystalline silica content in coal dust from coal fields in the USSR^a**

Coal field	Free silica content of airborne dust (%)
Doneck	
coal	1.7- 2.5
anthracite	2.0- 8.0
Karaganda	0.4-10.0
Kizelovsk	1.0-12.5
Moskva	
coal	0.8- 6.8
coal slate	16.0-28.0

^aFrom Huhrina & Tkachev (1968d)

36 mg/m³ carbon monoxide, 4 mg/m³ nitrogen oxides and 0.03 mg/m³ lead aerosol, averaged over the whole shift. The use of mechanized mining methods reduced mean total dust concentrations to 8 mg/m³, and the number of exposed workers was reduced by two to six fold (Menyailo & Getmanets, 1985).

In 1981-1982, total dust concentrations in the working zone of miners engaged in underground transport in two mines in the Doneck coal field (Table 13) fluctuated from 6.4 to 79 mg/m³. A maximal concentration of 113 mg/m³ was measured during the transportation of nonhumidified coal (Elez *et al.*, 1985).

Table 13. Airborne dust levels in the working zone of miners engaged in underground coal transport in the USSR^a

Mine	Occupation	No. of samples	Dust concentration (mg/m ³)	
			Range	Mean
Ayutinskaja	Operators of underground reloaders on slopes	48	9.5- 69.7	37.0
	Underground machine operators	16	4.1- 13.8	6.4
	Electric locomotive drivers	13	9.5- 64.6	26.0
	Operators of tipping equipment	36	6.4- 83	37.0
	Miners engaged in belt-conveyor cleaning	12	17.5-113	43.7
Krasnyj Sulin	Operators of underground equipment on belt inclines	145	6.7-111	79.0
	Electric locomotive drivers	6 ^b	-	46.0

^aFrom Elez *et al.* (1985)^bSampling with PI-1 personal samplers

Lower total dust concentrations were reported in mines in the high-humidity Moskva coal field: average concentrations on cutter-loader and heading machines with spraying devices did not exceed 34 mg/m³, and 40% of the samples were found to contain less than the maximal allowable concentration (10 mg/m³); in loading, 80-85% of the samples were also below this concentration (Huhrina & Tkachev, 1968d). Total dust concentrations in coal-processing factories were as high as 40-60 mg/m³, and at one conveyor transporting humidified coal the concentration was 10-40 mg/m³ (Huhrina & Tkachev, 1968e). At the Kansk-Ačinsk open-cast mine, mean concentrations of 0.2-4.2 mg/m³ were measured in operators' cabins and 8.8 mg/m³ on the platform of the transport belt excavator; 162 air samples were taken. The total dust (19-36% respirable fraction) contained 3.5% free crystalline silica (Borisenkova *et al.*, 1984).

During the mining of bituminous shale in the Estonian SSR, dust concentrations fluctuated from 1.4 to 7.2 mg/m³, the maxima being from 5.8 to 28.4 mg/m³ and the average from 4.6 to 13.6 mg/m³. The free crystalline silica content of the dust was 8.5%, and the silicate content ranged up to 15% (Huhrina & Tkachev, 1968d).

In a survey carried out at the Mecsek coal field (Hungary) in 1971-1974, the return air 8-16 m from the face contained respirable concentrations of 2.4-7.8 mg/m³, with an average free crystalline silica content of 4.2%, ranging from 2.5 to 5% (Vékény, 1976).

Total dust levels of 2-12 mg/m³ with an average quartz content of 9% were found in one Polish coal mine (Wałbrzych), but, in another (Sosnowiec), the concentrations were ten-fold higher, with a quartz content of 5% (Szymczykiewicz, 1981).

The quartz content of total dust in Bulgarian coal mines varied from 2.1 to 12.7%, with maximal values of up to 34.1% determined during drilling of rock. Average concentrations

SILICA

59

of total dust measured during the period 1960-1980 varied from 4 to 512 mg/m³; the respirable fraction constituted 10-20% of the total dust (Burilkov *et al.*, 1983c). Measurements in 1975-1985 showed average quartz contents of 1.5-18.2% in the total dust and 3.1-12.2% in the respirable dust. The average concentrations of respirable dust were 1.4-12.3 mg/m³, and those of respirable quartz 0.05-1.68 mg/m³ (Dobreva, 1986).

Granite and stone industry and construction work

Respirable silica levels to which workers in 54 granite industries in Vermont, USA, were exposed are summarized in Table 14. Mean exposures ranged from 0.01 mg/m³ for stencil cutters to 0.09 mg/m³ for sculptors and carvers; high exposures were also observed for polishers and sandblasters. The silica content of the respirable dust ranged from 4.8 to 12.2% (Peters *et al.*, 1972; Musk *et al.*, 1977).

Table 14. Respirable silica exposures in 54 granite industries in Vermont, USA, 1970^a

Job	No. of samples	Respirable silica exposure (mg/m ³) ^a		Silica in respirable dust (%)
		Mean	Range	
Cutter	117	0.06	<0.02-0.22	9.5
Sculptor, carver	16	0.09	0.02-0.28	10.5-12.2
Polisher	28	0.03	<0.02-0.12	6.2
Sandblaster	15	0.04	<0.02-0.10	7.3
Contour planer	19	0.02	<0.02-0.07	7.4
Wire sawyer	26	0.02	<0.02-0.10	6.0
Splitter	7	0.03	<0.02-0.06	7.9
Crane operator	3	0.02	0.01-0.03	5.0
Lumper (quarry work)	5	0.02	0.01-0.03	4.8
Stencil cutter	2	0.01	0.01-0.02	5.4
Finisher	21	0.05	<0.02-0.26	9.2
Grinder	7	0.01	<0.02-0.03	5.3

^aFrom Peters *et al.* (1972) and Musk *et al.* (1977); dust exposures rounded to the nearest 0.01 mg/m³

Respirable silica levels in five granite processing facilities in Vermont and 12 similar facilities in Georgia, USA, during 1973 and 1974 are reported in Table 15. Mean exposures in Vermont were found to range from 0.10 mg/m³ for stone cutters and saw operators to 0.07 mg/m³ for abrasive blasters, crane operators and other miscellaneous jobs. Respirable silica exposures in Georgia were found to be somewhat lower, with the highest average exposure 0.10 mg/m³ for saw operators. The average silica content of the respirable dust was 13.4% in Georgia and 13.0% in Vermont (Donaldson *et al.*, 1982).

Of 45 samples collected at building construction sites in 1972-1982 by the US Occupational Safety and Health Administration (see Table 23), 29% exceeded the US permissible silica exposure limit (0.10 mg/m³, see Table 7) by a factor of two or more.

Table 15. Respirable silica levels in granite industries in Vermont and Georgia, USA, 1973-1974^a

Job	Respirable silica (mg/m ³)			
	Vermont		Georgia	
	Mean (no. of samples)	Range	Mean (no. of samples)	Range
Lumper (quarry work)	0.08 (20)	0.02-0.18	0.04 (30)	0.01-0.16
Stone cutter	0.10 (42)	0.02-0.19	0.06 (61)	0.01-0.18
Saw operator	0.10 (34)	0.02-0.21	0.10 (29)	0.01-0.83
Polisher	0.08 (32)	0.02-0.17	0.09 (40)	0.01-0.36
Abrasives blaster	0.07 (29)	0.02-0.18	0.04 (17)	0.01-0.14
Crane operator	0.07 (12)	0.06-0.12	0.04 (32)	0.02-0.09
Miscellaneous jobs	0.07 (51)	0.01-0.18	0.05 (46)	0.01-0.22

^a From Donaldson *et al.* (1982); values rounded to nearest 0.01 mg/m³

Similar findings were obtained for construction work other than buildings. Exposures in excess of twice the permissible exposure standard were found in 27% of the 270 samples collected in cut stone and stone products industries (National Institute for Occupational Safety and Health, 1983).

In a study in the Swedish stone industry, the mean total dust concentration was found to be 18.9 mg/m³, with an average of 18% quartz in the respirable fraction (see Table 24). High dust levels were found during flame cutting (20.9 mg/m³), drilling (25.3 mg/m³), chiselling (23.9 mg/m³), dry grinding (42.1 mg/m³) and blasting (32.4 mg/m³) operations. Breathing zone samples for workers in drilling and transportation during tunnelling contained a mean of 11.8 mg/m³ total dust and 9-14% respirable quartz. They were also exposed to 4.8 mg/m³ oil mist (Gerhardsson *et al.*, 1974).

In Switzerland, high exposures to quartz were measured during drilling, chiselling and grinding of concrete during building construction (0.5-16.3 mg/m³ respirable dust, with 7-27% quartz) (Hodel, 1975).

In six slate factories in India, airborne levels in the workers' breathing zone were 11-177 mg/m³ total dust and 4-18 mg/m³ respirable dust. The quartz content of the respirable fraction was 48-61% (Saiyed *et al.*, 1985). Jade workers in Hong Kong were exposed to 1.0-5.6 mg/m³ total dust and 0.34-0.72 mg/m³ respirable dust during sawing, carving and polishing. The source of the high silica content (89%) in the respirable fraction during polishing was silica flour containing 97% crystalline silica (Ng *et al.*, 1985).

During construction of a water-power plant in the USSR, work place dust concentrations ranged from 25 to 196 mg/m³ in summer and from 1.6 to 69 mg/m³ in winter, with 17-85% free crystalline silica. People working in galleries were exposed to 24-202 mg/m³

SILICA

61

total dust containing 15-48% quartz. The air in the tunnels was also polluted by carbon monoxide (18-131 mg/m³), nitrogen oxides and radon (Babaev, 1980).

Average dust concentrations measured during construction work in Bulgaria are given in Table 16; workers in tunnelling were exposed to the highest concentration of respirable quartz (Burilkov *et al.*, 1983d). During road construction, average exposures to respirable dust were 0.51-94 mg/m³ and to total dust, 1.7-127 mg/m³. The highest concentrations were measured at quarries, asphalt plants and crushing-sorting stations. The free crystalline silica content of the total dust was 0.3-9.7% (Georgiev, 1984).

Table 16. Dust levels at construction and manufacturing sites in Bulgaria^a

Process	Concentration (mg/m ³)		
	Total dust	Respirable dust	Respirable quartz
Tunnelling	23.0	3.5	0.32
Quarrying	17.0	4.2	0.23
Manufacture of building materials			
Storage	14.5	1.8	0.07
Transport belts	50.0	5.0	0.11
Dosage	25.0	1.9	0.08
Charging of concrete agitators	12.9	1.3	0.07
Screening	14.9	1.3	0.03
Concrete agitators	26.0	2.1	0.07
Operators' cabs	29.1	3.6	0.10
Production of ceramic plates	41.3	4.4	0.15

^aFrom Burilkov *et al.* (1983d)

Ceramics, glass and related industries

Respirable silica exposures in two clay-pipe factories in North Carolina, USA (1974-1975) ranged from 0.01 to 0.20 mg/m³ (Anderson *et al.*, 1980).

Respirable silica levels in four brick factories in the USA are shown in Table 17. The mean free silica content of respirable dust in these plants was 9.1-14.2%. Workers were also potentially exposed to kaolin, pyrophyllite, silica frit, silica flour and feldspar frit, which were added or applied to the bricks before firing (Anderson *et al.*, 1980). Similar respirable silica levels (0.004-0.09 mg/m³) were reported in a plant producing refractory bricks (Salisbury & Melius, 1982).

The work-place concentrations of respirable dust in eight brick and two tile plants in Ontario, Canada, in 1970-1971 ranged from 1.1 to 4.3 mg/m³, with 7.5-21% crystalline silica (Rajhans & Budlovsky, 1972).

Table 17. Respirable silica concentrations in four brick factories in North Carolina, USA, 1974-1975^a

Job	No. of samples	Mean (mg/m ³)	Range (mg/m ³)
Loading raw materials	15	0.06	0.02-0.16
Grinding	18	0.08	0.03-0.16
Mixing	21	0.16	0.02-0.43
Brick making/pug mill	37	0.08	0.03-0.36
Kiln loading	20	0.05	0.01-0.12
Kiln unloading	12	0.11	0.02-0.38
Strapping/shipping	6	0.06	0.01-0.12
Fork truck operator	11	0.09	0.01-0.69
Administrative tasks	3	0.02	0.02-0.03
Miscellaneous	11	0.08	0.01-0.37

^aFrom Anderson *et al.* (1980); values rounded to nearest 0.01 mg/m³

Of 348 samples collected by the US Occupational Safety and Health Administration in industries manufacturing glass (see Table 23), 10% had silica concentrations two or more times the US permissible exposure standard (0.10 mg/m³; see Table 7). In factories producing structured clay products and pottery and other related products, 26 and 23%, respectively, of the samples contained more than twice the standard (National Institute for Occupational Safety and Health, 1983).

Of 33 dust samples taken from glass batch operations in four US fibrous glass plants, 10 (33%) had concentrations of respirable silica in excess of 0.10 mg/m³; concentrations ranged from <0.01 to 1.28 mg/m³. The percentage of silica in respirable dust varied from <1 to 50% (Dement & Zumwalde, 1972a,b; Dement *et al.*, 1972, 1973).

Levels of respirable crystalline silica in a US factory producing ceramic parts for electronic equipment ranged from none detected to 0.18 mg/m³. Of the 62 samples reported, nine (14.5%) contained more than 0.05 mg/m³. Cristobalite was not present in detectable concentrations in any sample (Pryor & Lilis, 1979).

In 1949, mass concentrations of total dust in a UK brick factory were reported to range from 4 to 257 mg/m³ during loading and emptying of kilns (Keatinge & Potter, 1949). In a modern pottery, the exposure of fettlers averaged 0.80 mg/m³ respirable dust. A typical vitreous china product contained 25% flint, 25% china clay, 25% ball clay and 25% feldspar. The quartz content was lower in the respirable dust (mean, 15.1%) than in the material that was handled (27%) (Higgins *et al.*, 1985).

In 17 cement factories in Italy, the median respirable dust concentration was about 3 mg/m³ during bagging, about 7 mg/m³ in storage areas, 1.5 mg/m³ in control rooms and 0.9 mg/m³ at other sites. Most samples contained less than 1% free silica (Pozzoli *et al.*, 1979). In a factory producing refractory bricks, respirable dust levels ranged from 0.25-1.65 mg/m³, with a quartz content of 6-30% in various manufacturing processes (Puntoni *et al.*, 1985).

In Swedish glass, porcelain and cement factories, mean total dust concentrations were 13.3, 7.1 and 61.2 mg/m³, respectively. In these industries, the mean quartz content in respirable dust ranged from 4 to 9% (see Table 24; Gerhardsson *et al.*, 1974).

In high-temperature refractory brick (chamotte) plants in the USSR in 1972, the average concentrations of total dust were 3.8-13.1 mg/m³ in winter and 3.3-8.8 mg/m³ during the summer; the free silica content of the dust was 10-30%. Measurements were taken during milling, press forming and kiln firing. In two studies in 1966-1971 and 1972-1978 in a factory producing insulating tiles (dina), the average concentration of total dust was 1.4-1.5 mg/m³, with 90% free silica (Lemyasev *et al.*, 1976, 1981).

The average total dust concentrations of 163 samples taken during diamond cutting and polishing of crystal glass in the USSR was 8 mg/m³, with a range of 2.1-17.3 mg/m³, and with an amorphous silica content of 16-43% (Puchezhsky *et al.*, 1981).

Measurements in two cement plants in the USSR using wet-processing technologies showed an average total dust concentration of 5.4 mg/m³ in one and 83 mg/m³ in the other. In dry-manufacturing processes, the dust concentrations were higher (326 mg/m³). The free silica content in the cement dusts was less than 2% (Huhrina & Tkachev, 1968f).

Measurements performed by the Hygienic and Epidemiological Inspectorates in Bulgaria during the period 1976-1983 in ceramics factories showed high dust concentrations: 12.4-56.0 mg/m³ total dust and 1.0-4.0 mg/m³ respirable dust. The free crystalline silica content varied from 2.1 to 12.2% in total dust and from 1.6 to 12.0% in respirable dust. High levels were measured during the storage and transportation of raw materials (22 mg/m³), during crushing and milling (83 mg/m³), in mixing (12 mg/m³), in moulding (16 mg/m³), in drying and firing (94 mg/m³) and in sorting and loading (53 mg/m³) operations (Burilkov *et al.*, 1983e; Dobreva, 1986).

Exposure levels during the quarrying, crushing and mixing of quartzite for production of dina insulating tiles in Bulgaria ranged from 0.5 to 16.4 mg/m³ respirable dust, with a free crystalline silica content of 17-72% (Dobreva, 1986).

Dust concentrations in the Bulgarian porcelain industry for the period 1969-1980 are shown in Table 18. The respirable fraction averaged 26% of the total dust. Dust in a factory producing high-temperature refractory materials (chamotte) has been reported to contain 2.6-12.3% cristobalite (Burilkov *et al.*, 1983e).

The average total dust concentrations and free crystalline silica contents in dust to which workers in the Bulgarian glass industry were exposed in 1969-1982 are given in Table 19. The highest concentrations were measured during the preparation of raw materials and during frosting of glassware. The free crystalline silica content in the dust varied from 10.4 to 20.5%, whereas the respirable fraction ranged from 3 to 10% of total dust. On average, silica glass smelters were exposed to 14.1 mg/m³ total dust and 1.5 mg/m³ respirable dust which contained about 1.5% quartz and 69% amorphous silica (Burilkov *et al.*, 1983e).

Dust concentrations measured during cement production in Bulgaria in 1975-1977 are given in Table 20. The measurements showed that, even if the percentage of free crystalline silica in the dust is low, the level of respirable free crystalline silica may still be as high as 0.46 mg/m³ (Burilkov *et al.*, 1983f).

Table 18. Mean total dust concentrations and free crystalline silica contents in porcelain production in Bulgaria 1969-1980^a

Process	Mean total dust concentration (mg/m ³)	Free crystalline silica content (%)
Raw material storage and transport	43	5.2
Raw material preparation, dosage and milling	44	13.2
Clay batch making	57	8.1
Moulding	26	17.2
Biscuit baking	4	2.9
Air blasting	16	14.1
Glazing	20	5.3
Glaze baking	2	3.6
Grinding	30	4.8
Packing and storage	3	3.8
Plaster moulds making	33	—
Chamotte making	47	7.7

^aFrom Burilkov *et al.* (1983e)**Table 19. Average total dust concentrations and free crystalline silica contents in dust in glass production in Bulgaria (1969-1982)^a**

Operation	Average total dust concentration (mg/m ³)	Free crystalline silica content (%)
Raw materials unloading and storage	131	11.1
Raw materials milling and screening	101	20.5
Drying of sand	114	19.3
Sand-batch ingredient dosage	95	13.0
Sand-batch mixing	68	10.6
Kiln charging	25	10.4
Moulding of ware	3	15.5
Grinding, polishing, engraving	19	—
Frosting	84	20.2
Plate-glass breaking and cutting	6	15.3
Packing and storage	9	—

^aFrom Burilkov *et al.* (1983e)

SILICA

65

Table 20. Dust levels in dry manufacturing processes in cement plants in Bulgaria, 1975-1977^a

Operation	Concentration (mg/m ³)			Free crystalline silica content (%)	
	Total dust	Respirable dust	Respirable quartz	Total dust	Respirable dust
Quarrying of raw materials	21	9.9	0.46	5.7	2.0
Crushing of materials	22	5.7	—	5.0	—
Belt transport	99	11.6	0.20	4.7	—
Milling of raw materials					
feeding of mills	118	8.7	0.01	4.3	0.18
transport	162	24.6	—	3.3	1.8
automated weighing	286	8.9	0.19	5.6	1.8
milling	22	3.0	—	4.3	—
control board	10	2.5	—	5.8	—
Kilns for cement clinker	38	8.1	0.09	4.7	0.4
Clinker milling					
automated weighing	122	3.2	—	3.2	—
control board	9	3.9	—	2.9	—
Packing					
waggon filling	145	3.1	—	2.3	—
sack filling	68	7.1	—	2.7	—
truck loading	132	7.4	—	2.6	—
Raw material storehouses					
transport belt charging	51	—	—	3.5	—

^aFrom Burilkov *et al.* (1983f)*Amorphous silica industries*

Diatomaceous earth is a natural form of amorphous silica, but when it is heated to high temperatures during calcining, cristobalite is formed. The cristobalite content of diatomite in a US diatomaceous earth processing plant was <1% when uncalcined, 10-20% when straight-calcined and 40-60% when flux-calcined. Although actual dust levels were not reported, respirable dust exposures to natural, straight-calcined and flux-calcined diatomite were <1.05, 0.21 and 0.14 mg/m³, respectively (Cooper & Jacobson, 1977).

In Iceland, occupational exposure to respirable dust during diatomite mining and processing ranged from 0.1 to 2.0 mg/m³. The airborne dust contained less than 5% quartz, but some calcined products had a cristobalite content of 75% (Reimannsson, 1981). In a Swedish production plant, the average concentration of respirable diatomite dust was 28.2 mg/m³, with a quartz content of 4% (Gerhardsson *et al.*, 1974).

In a factory producing and bagging Aerosil (highly dispersed, chemically pure, amorphous silica) in the Federal Republic of Germany, total dust concentrations were

2-7 mg/m³. The airborne dust was composed mainly of amorphous silica particles about 0.02 µm in diameter (Volk, 1960).

Foundries and metallurgical industries

Exposures to silica and to metal fumes, carbon monoxide and polynuclear aromatic compounds in iron and steel foundries were reviewed by a previous working group (IARC, 1984). Only information additional to that reported earlier is given in this section.

The median silica content of respirable dust in 1743 personal air samples collected by the US Occupational Safety and Health Administration in US foundries between 1976 and 1981 ranged from 7.3 to 12.0%; during melting, 56.4% of the samples had more than 0.12 mg/m³ respirable silica. Workers in ferrous foundries generally had higher exposures than those in nonferrous foundries (Oudiz *et al.*, 1983). These results are similar to those shown in Table 23, where 23% of the 10 850 samples collected in iron and steel foundries had concentrations in excess of approximately 0.20 mg/m³ respirable silica (National Institute for Occupational Safety and Health, 1983).

The free silica content of respirable dust in the work environment in nine foundries in Alberta, Canada, in 1978-1980 was found to range from 3 to 25%; in three of the foundries, cristobalite was detected. Respirable dust levels were compared with the applicable time-weighted average silica dust standard [calculated from the formula: 10 mg/m³/(% SiO₂ + 2)]. The ratio of actual levels to the dust standard in the moulding process was 0.50 to 3.4 in foundries considered to have 'good' controls; levels in operations with no dust control were generally in excess of the exposure standard. Uncontrolled shake-out operations were found to generate exposures as high as 21 times the standard (Ayalp & Myroniuk, 1982).

Total dust levels measured during ferrosilicon production ranged from 0.6 to 66 mg/m³ in an Italian plant in 1962-1966 (Corsi & Piazza, 1970), from 2.1 to 26 mg/m³ in a factory in the Federal Republic of Germany in 1968 and 1970 (Prochazka, 1971) and averaged 23 mg/m³ in a Swedish plant (Gerhardsson *et al.*, 1974). The dust in the German factory was composed mainly of amorphous silica, but it also contained 5-21% crystalline forms (Prochazka, 1971).

In the Norwegian ferroalloy industry, total average dust exposures ranging from 2-64 mg/m³ have been observed, with respirable dust making up 25-65%. Generally, the crystalline silica content was <2%, but during handling of raw material the quartz content reached 50%. The content of amorphous silica was 10-65% (Kjuus & Langård, 1984).

Studies carried out in a Bulgarian ferroalloy plant showed average concentrations of 8.7-51.0 mg/m³ for total dust, 1.2-6.2 mg/m³ for respirable dust and 0.12 mg/m³ for respirable quartz. The concentration of respirable amorphous silica was 0.5-3.1 mg/m³ (Lukanova *et al.*, 1979).

In open-hearth steel works in the USSR, average total dust concentrations ranged from 1.4 to 20.2 mg/m³ in 164 work-area samples. The free crystalline silica content of the dust was 1.4-2.5%; it also contained manganese, chromium, vanadium and molybdenum oxides. The chromic oxide concentrations in air varied from 13.2 to 37.1 mg/m³ (Belitskaya, 1981).

In the batch-preparing shop of a copper metallurgic plant in the USSR, total dust concentrations were 5.4-18.5 mg/m³, with a quartz content of 8%. More than 20 elements

SILICA

67

were found in the dust, including copper, lead and zinc. During some work processes, 21-24 mg/m³ carbon monoxide and 66 mg/m³ higher alcohols were also measured (Borisov, 1980). In large copper-smelting plants in Kazakhstan, total dust concentrations were 5.0-7.3 mg/m³ (Liakh, 1979).

Seventy-five samples of dust taken from various foundry operations in the German Democratic Republic had average concentrations of 4.7 mg/m³ total dust and 0.8 mg/m³ respirable dust, with free crystalline silica contents of 19 and 13%, respectively (Duve & Tkachev, 1982).

In 1967-1970, the average silica content of total dust in Bulgarian foundries varied from 13 to 23% and reached a maximum of 78% in some processes. In older foundries, mean concentrations of total dust were as high as 60 mg/m³. Table 21 gives mean concentrations of total and respirable dust and respirable quartz in some large foundries in Bulgaria. Exposures to respirable free crystalline silica varied widely, from 0.01 to 2.75 mg/m³. The free silica content of the respirable dust ranged from 3.7 to 20.7%. Workers engaged in sand preparation were exposed to the highest concentrations of respirable free crystalline silica, followed by workers in fettling, moulding and core-making operations (Burilkov *et al.*, 1983g).

Miscellaneous silica exposures

Sandblasters and associated workers have been known to be at high risk of developing silicosis, sometimes within a relatively short period of employment. Exposures of sandblasters and associated personnel, by silica concentration, in two steel fabrication yards in the USA are shown in Table 22. Silica concentrations in the breathing zone averaged 4.8 mg/m³ for sandblasters and 0.7 mg/m³ for helpers. All personnel except crane drivers were found to have mean exposures in excess of 0.10 mg/m³ (Samimi *et al.*, 1974). Silica concentrations inside hoods with no air supply were 0.4-7.7 mg/m³ (Samimi *et al.*, 1975).

Respirable silica concentrations greater than 0.05 mg/m³ were reported for five of 14 samples taken in a US factory manufacturing abrasive chips to deburr and polish metal parts. The highest exposures were reported during batch mixing and inspection, and packaging. The silica content of the respirable dust was found to be 0.4-5.8% (Apol, 1973).

Miscellaneous exposures to silica in US industries are included in Table 23 (National Institute for Occupational Safety and Health, 1983) and those in Sweden in Table 24 (Gerhardsson *et al.*, 1974).

A median total dust concentration of 7-40 mg/m³ was measured during ploughing and harvesting in the Federal Republic of Germany. The respirable dust contained <1-25% quartz (Batel, 1979).

Loggers working around Mount St Helen's, WA, USA, after volcanic activity, were exposed to respirable dust in concentrations of 0.09-1.20 mg/m³; the respirable dust contained 3-7% free silica (quartz, cristobalite and possibly tridymite) (Merchant *et al.*, 1982).

Table 21. Dust concentrations in iron and steel foundries in Bulgaria^a

Foundry type and operation	Dust concentration (mg/m ³) (range)		
	Total dust	Respirable dust	Respirable free crystalline silica
Steel foundry			
sand drying	51.3	7.4	2.75
sand screening	23.1	2.2	0.60
edge milling	8.6	1.2	0.20
moulding	2.1	1.2	0.30
core-making	1.6	0.8	0.10
shake-out	6.0	1.7	0.25
transportation	12.6	2.9	0.50
arc cutting	7.1	1.2	0.10
grit blasting	17.4	1.4	1.10
cleaning by grinding	11.9	1.5	0.30
pneumatic cleaning	8.7	2.1	0.70
Iron foundry at an agricultural machinery plant			
moulding	8.6	0.95	0.03
pouring	3.0	0.80	0.01
loading of waggons	14.2	3.83	0.45
manual shake-out	18.3	13.12	0.42
cleaning by grinding	15.6	2.78	0.03
Iron foundry at a railroad machinery plant			
cleaning by grinding	9.0	1.10	0.09
stationary grinding	25.1	3.20	1.00
Iron and steel foundries			
preparing foundry sand	44.2 (31.5-84.5)	8.7 (1.8-13.2)	1.01 (0.19-1.8)
moulding	18.2 (9.8-30.2)	2.6 (2.0-4.0)	0.26 (0.13-0.39)
cleaning castings	34.2 (17.0-52.6)	5.8 (1.9-9.2)	0.92 (0.08-1.04)
core making	15.6 (5.2-17.4)	2.3 (0.65-2.06)	0.19 (0.05-0.50)

^aFrom Burilkov *et al.* (1983g) and Dobreva (1986)

SILICA

69

Table 22. Respirable free silica levels in sandblasting and associated operations in the USA^a

Occupation	No. of samples	Concentration of respirable silica (mg/m ³)	
		Mean	Range
Sandblasters ^b	63	4.77	<0.01-43
Helpers	1	0.71	—
Pot handlers	18	0.30	0.02-0.86
Painters	4	0.18	0.07-0.30
Welders	26	0.20	0.01-2.10
Crane drivers	15	0.06	<0.01-0.43
Other workers	20	0.12	0.01-0.35

^aFrom Samimi *et al.* (1974)^bThe concentrations are overall averages of samples taken inside and outside protective hoods and do not represent the actual exposure of workers.**Table 23. Respirable silica exposures in US industries, 1972-1982^a**

Industry or standard industrial classification	No. of samples	% of samples >twice PEL ^b
Agriculture, forestry and fishing	43	63
Mining	43	57
Construction		
Building construction — general contractors	45	29
Construction other than building construction — general contractors	424	30
Construction — special trade contractors	289	10
Manufacturing		
Food and allied products	187	52
Textile mill products	52	27
Apparel and other finished products	16	0
Lumber and wood products, except furniture	13	8
Furniture and fixtures	31	0
Paper and allied products	82	13
Printing, publishing and allied industries	31	0
Chemicals and allied products	640	13
Petroleum refining and related industries	214	11
Rubber and miscellaneous plastic products	269	9
Leather and leather products	14	0
Flat glass	82	9
Glassware, pressed or blown	229	11
Glass products from purchased glass	37	11
Hydraulic cement	65	0
Structured clay products	635	26

Table 23 (contd)

Industry or standard industrial classification	No. of samples	% of samples >twice PEL ^b
Pottery and related products	945	23
Concrete, gypsum and plaster products	347	12
Cut stone and stone products	270	27
Abrasives, asbestos and miscellaneous nonmetallic mineral products	558	16
Primary metal industries		
Blast furnace, steel works, rolling and finishing mills	639	32
Iron and steel foundries	10850	23
Primary smelting and refining of nonferrous metals	146	9
Secondary smelting and refining of nonferrous metals	39	0
Rolling, drawing and extruding of nonferrous metals	23	22
Nonferrous foundries (casting)	2170	9
Miscellaneous primary metal products	68	46
Fabricated metal products, except machinery and transportation equipment	1265	22
Machinery, except electrical	1377	13
Electrical and electrical machinery equipment and supplies	474	23
Transportation equipment	600	20
Measuring, analysing and controlling instruments, photographic, medical	137	36
Miscellaneous manufacturing industries	211	9
All other industries	460	15

^aFrom National Institute for Occupational Safety and Health (1983)^bPEL, permissible exposure limit, calculated from the formula: $10 \text{ mg/m}^3 / (\% \text{ SiO}_2 + 2)$ **Table 24. Dust levels in Swedish industries, 1968-1971**

Industry or operation	No. of workers studied	Mean total dust concentration (mg/m^3)	Mean quartz concentration in respirable dust ^b (%)
Mining			
underground	124	8.4	7
surface	249	5.9	7
Quartz	65	4.5	46
Stone	381	18.9	18
Stone quarries	226	24.1	21
Gravel quarries	402	9.3	24

Table 24 (contd)

Industry or operation	No. of workers studied	Mean total dust concentration (mg/m ³)	Mean quartz concentration in respirable dust ^b (%)
Tunnelling	70	11.8	17
Steel production	195	17.3	9
Steel foundries			
quartz sand moulding	54	8.8	12
olivine sand moulding	38	12.4	5
Iron foundries	821	19.5	12
Other metal foundries	185	12.1	13
Ceramics			
porcelain	46	7.1	9
other ceramics	58	8.2	11
Glass	52	13.3	8
Abrasives			
grinding wheels	31	5.5	5
grinding paper and cloth	9	8.0	42
polishing materials	5	2.8	46
Lime and dolomite	11	51.2	2
Bricks	26	5.8	17
Cement	32	61.2	4
Concrete	34	5.9	8
Roofing felt	14	71.6	4
Asphalt	65	9.7	16
Rubber	24	35.1	1
Paint	20	14.1	13
Scouring powder	9	18.7	47
Sandblasting	67	39.2	44
Welding electrode	8	6.3	12
Potato chip manufacture	20	6.8	13
Road sweeping	7	12.8	13

^aFrom Gerhardsson *et al.* (1974); a total of 3715 exposure measurements made in 1059 work places

^bThe mean respirable fraction (the mass % of particles < 5 µm) ranged from 12 to 56%.

(c) Nonoccupational exposures

Quartz occurs as particles suspended in water at concentrations that are largely a function of rock type and the quartz content of the geological formation through which the water flows. Quartz is the most stable mineral in the geochemical environment of the Earth's surface and is therefore among the most common minerals in detrital waterborne sediments (Murphy & Henderson, 1983).

Diatoms occur in both fresh and salt water. Langer *et al.* (1979) reported their presence in potable water drawn from Lake Superior in the USA. Opaline diatom fragments are present in drinking-water around the world and may be ingested on a daily basis. The

quantities of silica ingested from drinking-water containing diatoms have not been reported.

Local conditions, especially in deserts and areas around recent volcanic eruptions and mine dumps, can give rise to airborne silica-containing dust. Data on 'free silica' in air are generally derived indirectly. For example, it has been reported that 'environmental silicosis' occurs among the Bedouins of the Negev Desert (Bar-Ziv & Goldberg, 1974). Quantities of airborne dust originating from world deserts have been reported by Péwé (1981), who estimated that 4.5×10^8 tonnes are shifted annually to new depositional sites. The mineral varieties range considerably and are only in part free silica. Merchant *et al.* (1982) found 3-7% free silica in ash samples after the eruption of Mount St Helens, WA, USA.

Silica and its common forms are found in a large number of consumer products. Some, such as consumer talcs, may be derived from crushed rocks (Rohl *et al.*, 1976); others may be formulated by blending of minerals, as for spackling, patching and taping compounds used in dry-wall construction (Rohl *et al.*, 1975). Amorphous silica has also been used in carrier materials for pharmaceutical tablets (Gottschewski, 1967).

Silica is also found as an unintentional contaminant. For example, diatomaceous earth has been used as a filler in reconstituted tobacco sheets used in the manufacture of smoking articles. The opaline form may be partly converted to cristobalite as it passes through the burning tip (Langer *et al.*, 1971).

2.3 Analysis

Dust sampling methods have been reviewed by the World Health Organization (1984) and by the US National Institute for Occupational Safety and Health (1974).

Silica can be analysed by a number of techniques, including optical microscopy, analytical electron microscopy, differential thermal analysis, infrared spectrometry, wet chemical techniques and X-ray diffraction (World Health Organization, 1984). However, for quantitative evaluation of occupational exposure, infrared spectrometry and X-ray diffraction are the preferred techniques (Pickard *et al.*, 1985). Wet chemical techniques are usually used to determine total silica and do not distinguish amorphous and crystalline forms.

For dust samples taken in a wide range of industrial environments, the choice of analytical wave-lengths in infrared spectrometry is limited by the presence of interfering substances. Absorption peaks at 695, 780 and 799 cm^{-1} are used to determine quartz. Peaks at 780-800 cm^{-1} are used to analyse both amorphous and crystalline silica. The detection limit for crystalline silica (e.g., quartz) is approximately 50 μg , which represents an atmospheric level of 0.1 mg/m³ for a 0.5-m³ air sample. The method for detecting amorphous silica is less sensitive. The two forms interfere, but in fused silica they can be analysed separately (Dodgson & Whittaker, 1973; Lukanova, 1977; Bye *et al.*, 1980).

X-ray diffraction is used to determine crystalline varieties of silica. Analysis for silica polymorphs in a powdered mixture by X-ray diffraction is dependent upon the particle size of the components and matrix characteristics; therefore, internal or external standards are needed to compensate for the variation in dust samples. By continuous scanning, 1-5%

quartz can be determined in a mineral matrix; step-scanning techniques, for specific reflections, may improve sensitivity to detect about 1% (Rohl *et al.*, 1976).

In X-ray diffraction, the strongest reflections most commonly used to analyse for silica are (Dunnom, 1984):

quartz	0.334 nm	0.426 nm	0.182 nm
cristobalite	0.405 nm	0.249 nm	0.284 nm
tridymite	0.411 nm	0.433 nm	0.382 nm

The detection limit in respirable dust samples is about 5 µg for quartz and 10 µg for cristobalite, which approximates an atmospheric level of 0.01-0.02 mg/m³ for a 0.5-m³ air sample (Bye *et al.*, 1980, Bye, 1983).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals¹

Crystalline silica

(a) Inhalation exposure

Mouse: A group of 60 female BALB/cBYJ mice, six weeks old, was exposed by inhalation in chambers to quartz (as Min-U-Sil, a crystalline silica containing more than 96% quartz from Pennsylvania Glass and Sand Co.) for 8 h per day on five days per week. Subgroups of six to 16 mice each were exposed for total periods of 150, 300 or 570 days, and were necropsied either immediately after the end of the exposure period or following a holding period of 30 or 150 days. The concentrations of particles <1.2 µm in diameter were 1475, 1800 and 1950 µg/m³ for the groups exposed for 150, 300 and 570 days, respectively. A similar group of 59 controls received no exposure to silica but was sacrificed by the same schedule. Pulmonary adenomas were found in both silica-exposed and control groups; their incidences (9/60 and 7/59) showed no statistically significant difference (Wilson *et al.*, 1986). [The Working Group noted the small number of animals in each exposure group.]

Rat: Groups of 72 male and 72 female Charles River Fischer 344 rats, three months old, were exposed by inhalation in chambers to 0 or 51.6 mg/m³ quartz as Min-U-Sil (particle size: mass median aerodynamic diameter, 1.7-2.5 µm; geometric standard deviation, 1.9-2.1) in air for 6 h per day on five days per week for 24 months. After four, eight, 12 and 16 months of the experiment, ten males and ten females per group were removed; five were sacrificed and five were retained with no further exposure. All survivors were killed at 24 months. Mean survival was 781 ± 12.8 days for controls and 632 ± 5.7 days for rats exposed to quartz until death (22 males and 22 females per group). The incidence of epidermoid carcinomas of the lungs in treated rats still alive at 494 days, when the first tumour appeared,

¹The Working Group was aware of a study in progress in rats by intrapleural administration (IARC, 1986).

was 10/53 (19%) females and 1/47 (2%) males. Three of five female rats receiving no further exposure to quartz after four months also developed epidermoid carcinomas; metastasis to the lymph nodes was reported in one rat. None of the 42 male or 47 female controls developed a lung tumour. Additional lesions in quartz-treated rats included areas of pulmonary adenomatosis, cuboidal metaplasia of the alveolar epithelium, as well as alveolar proteinosis, lymphoreticular hyperplasia and nodular fibrosis (Dagle *et al.*, 1986). [The Working Group noted that, due to inadequate reporting, it cannot be determined from which exposure groups animals surviving at 494 days were derived.]

Groups of 62 female Charles River Fischer 344 rats were exposed by nose-only inhalation to $12 \pm 5 \text{ mg/m}^3$ quartz as Min-U-Sil aerosol (particle size: mean geometric size, $2.0 \pm 0.2 \mu\text{m}$; all particles $<5.0 \mu\text{m}$) for 6 h per day on four days per week for 83 weeks and were observed for the duration of their lifespan. Controls were sham-exposed to filtered air (62 females) or unexposed (15 females). Mean survival time was 683 ± 108 days for quartz-exposed rats and 761 ± 138 days for sham-exposed controls. [The survival time of the unexposed controls was unspecified.] Of the quartz-exposed rats, 18/60 had lung tumours (three squamous-cell carcinomas, 11 adenocarcinomas and six adenomas), all of which were observed after 17 months or more of exposure. No lung tumour was observed in 54 surviving sham-exposed controls; 1/15 unexposed controls had an adenoma of the lung. Most of the quartz-exposed rats still alive after 400 days developed pronounced pulmonary fibrosis, lung granulomas and silicotic nodules, often accompanied by emphysema and alveolar proteinosis (Holland *et al.*, 1983, 1986). A morphological description of the tumours is given by Johnson *et al.* (1987).

(b) *Intratracheal administration*

Rat: A group of 40 Sprague-Dawley rats [sex and age unspecified] received weekly intratracheal instillations of 7 mg quartz as Min-U-Sil (mean particle size, $1.7 \mu\text{m}$; all particles $<5 \mu\text{m}$) in 0.2 ml saline for ten weeks. A group of 40 rats received saline only and another group of 20 animals was untreated. All animals were observed for the duration of their lifespan. [Survival rates were unspecified.] Lung tumours were reported in 6/36 quartz-treated rats (one adenoma and five carcinomas); no such tumour was observed in either 40 saline or 18 untreated controls. Fibrotic lesions were also observed in quartz-treated animals (Holland *et al.*, 1983).

Groups of 85 male Charles River Fischer 344 rats, obtained when weighing $180 \pm 15 \text{ g}$ and treated two weeks later, received a single intratracheal instillation of 20 mg quartz into the left lung as Min-U-Sil (particle size, $0.1\% \geq 5 \mu\text{m}$; surface area, $4.3 \text{ m}^2/\text{g}$) or as Novaculite (particle size, $2.2\% \geq 5 \mu\text{m}$; surface area, $1.6 \text{ m}^2/\text{g}$) in a suspension of filtered, deionized water [volume unspecified]. Controls received the suspension vehicle alone. Interim sacrifices of ten rats each were made at six, 12 and 18 months; terminal sacrifice was made at 22 months. In the Min-U-Sil-treated group, the incidences of lung carcinomas were 1/10 at 12 months, 5/10 at 18 months, 5/17 in rats that died between 12–22 months, and 19/30 at 22 months; total incidence was 30/67 (45%). All tumours were adenocarcinomas, some of which had squamous and/or undifferentiated areas. The incidences of lung carcinomas in the Novaculite-treated group were: 1/10, 2/10, 2/17 and 16/35, respectively.

(total incidence, 21/72; 29%); one carcinoma was of the epidermoid type, all the others were adenocarcinomas; 87% of the tumours were in the left lobe. In the control group, 1/44 animals had an adenocarcinoma at 22 months (total incidence, 1/75). The Min-U-Sil-treated group had larger tumours and more extensive granulomatous and fibrotic lesions than the Novaculite-treated group (Groth *et al.*, 1986).

Hamster: Two groups of 48 Syrian golden hamsters [sex and age unspecified] received intratracheal instillations of 3 or 7 mg quartz as Min-U-Sil (mean particle size, 1.71 μm) in 0.2 ml saline once weekly for ten weeks. A group of 68 animals received saline only, and another group of 72 animals was untreated. All animals were observed for the duration of their lifespan. No lung tumour was observed among 31 low-dose animals, 41 high-dose animals, 58 saline controls or 36 untreated controls. The incidence and severity of pulmonary fibrosis was minimal. Pneumonitis-pneumonia complex occurred in 13/31 and 21/41 of animals receiving the low and high dose, respectively, late in the exposure period (Holland *et al.*, 1983). [The Working Group noted that survival rates were not specified.]

Groups of 25-27 male outbred Syrian golden hamsters (Lak:LVG, Lakeview), 11 weeks old, received weekly intratracheal instillations of 0.03, 0.33, 3.3 or 6.0 mg quartz as Min-U-Sil (average particle diameter, 1.06 μm) in saline [volume unspecified] for 15 weeks. Groups of 27 saline-treated and 25 untreated controls were available. Animals were killed when moribund or when survival within the group reached 20%; terminal sacrifice was at 24.5 months of age. The average survival times were 498, 506, 383 and 348 days for the quartz-treated groups, respectively, and 534 and 595 days for the saline and untreated controls, respectively. A further four groups received the same treatment with quartz to which an equal dose of ferric oxide had been added. Average survival times were 558, 578, 379 and 335 days in the four dose groups, respectively. In animals treated with quartz or quartz plus ferric oxide, dose-related alveolar septal fibrosis (of slight to moderate degree), granulomatous inflammation and alveolar proteinosis were observed in the lungs. No animal developed nodular fibrosis or foci of dense fibrous tissue. No tumour was observed in any of the groups (Renne *et al.*, 1985).

Two groups of 50 male outbred Syrian golden hamsters, seven to nine weeks old, received weekly intratracheal instillations of 0.7 mg of the respirable fraction of Min-U-Sil or 1.1 mg Sil-Co-Sil (silica sand, from Ottawa Silica Co.) in 0.2 ml saline for 15 weeks. Survivors were killed 92 weeks after the first treatment. A group of 50 controls received instillations of 0.2 ml saline alone. One adenosquamous carcinoma of the bronchi and lung was observed at 68 weeks among the 35 survivors given Min-U-Sil; no respiratory tumour was observed in the 50 animals treated with Sil-Co-Sil or in 48 controls. For comparison, groups of 50 male hamsters received weekly intratracheal instillations of 3.0 mg ferric oxide or 0.7 mg Min-U-Sil plus 3.0 mg ferric oxide. In the ferric oxide-treated group, one benign tumour of the larynx was observed among 34 survivors at 62 weeks; no respiratory-tract tumour was observed in the 49 animals treated with quartz plus ferric oxide (Niemeier *et al.*, 1986).

(c) *Intrapulmonary deposition*

Rabbit: A group of seven common rabbits [sex unspecified], weighing 1550-2350 g, received an intrapulmonary deposit of quartz (particle size, about 2 μm) [quantity

unspecified] suspended in 0.5 ml saline. Two animals died post-operatively. Of the five remaining rabbits that survived five to six years, four developed malignant lung tumours: three adenocarcinomas involving both lungs and one sarcoma involving the pleura. No silicotic lesion was found, but fibrous capsules were formed around the quartz deposits. Epithelial hyperplasia and metaplasia were observed in the peripheral airways (Kahlau, 1961). [The Working Group noted the small number of animals used and the lack of vehicle controls.]

(d) Intrapleural and intrathoracic administration

Mouse: In a study reported as an abstract, groups of 37-43 male Marsh mice, three months of age, received a single intrathoracic injection of 10 mg tridymite (particle size, 20% <3.3 µm and 40% in the range 6.6-15 µm; heavy metal and iron content, 0.002%) in saline or 5 mg chrysotile (acid washed, containing 0.4% iron and 0.05% copper), or saline alone. After 19 months, the effective numbers of mice were 32-34 per group. Animals given tridymite developed one lung adenocarcinoma and two intrapleural lymphoid tumours; there was one lung adenocarcinoma and no lymphoid tumour in saline controls, and four lung adenocarcinomas and four lymphoid tumours in the chrysotile group. Lesions reported as 'lymph node reactive hyperplasia simulating malignancy' were found in 19/32 tridymite-, 1/34 saline- and 1/32 chrysotile-treated mice (Bryson *et al.*, 1974).

Rat: Groups of 48 male and 48 female SPF Wistar rats or standard Wistar rats, six weeks of age, received a single intrapleural injection (right axilla) of 0.4 ml saline alone or 0.4 ml saline containing 20 mg quartz particles (alkaline-washed quartz; particle size, <5 µm; from Safety in Mines Research Establishment, Sheffield, UK) and were observed for their lifespan. The 50% survival of quartz-treated SPF rats was nearly 850 days and that of standard rats nearly 700 days. Malignant tumours of the reticuloendothelial system involving the thoracic region were observed in both SPF (39/95; 23 with histiocytic lymphoma) and standard rats (31/94; 30 with histiocytic lymphoma) treated with silica compared to 8/96 and 7/85 (no histiocytic lymphoma) standard saline-treated controls. These tumours were observed in the upper mediastinum, the pericardium and diaphragm, the lungs and, to a lesser extent, the pleura, the liver and the spleen. The distribution of malignant tissue corresponded to that of silicotic nodules. A variety of other tumours did not appear to be associated with treatment. Standard rats often had accompanying infections that were absent in the SPF rats (Wagner & Wagner, 1972). [Additional data are given by Wagner & Berry (1969) and Wagner (1970)].

These results were confirmed in a larger study. A total of 23 malignant reticulothelial tumours (21 malignant lymphomas, histiocytic type — MLHT) were observed in a group of 80 male and 80 female caesarean-derived SPF inbred Wistar rats, six weeks of age, that received a single intrapleural administration (right axilla) of 20 mg of the same quartz particles in 0.4 ml saline. Two males and two females were sacrificed every five weeks up to 120 weeks. No MLHT and one thymoma/lymphosarcoma occurred in a group of 15 saline controls (Wagner, 1976).

A group of 16 male and 16 female caesarean-derived SPF inbred Wistar rats, six weeks of age, received a single intrapleural administration (right axilla) of 20 mg quartz as

SILICA

77

Min-U-Sil (99% pure) in 0.4 ml saline. The animals were killed when moribund (mean survival, 678 days). Eight of 32 rats developed MLHT, and 3/32 developed thymoma/lymphosarcoma. In 15 controls treated with saline only, no MLHT but one thymoma/lymphosarcoma was found (mean survival, 720 days). In 16 rats treated with respirable size coal dust in saline (mean survival, 690 days) and in 16 rats treated with carbon black dust in saline (mean survival, 618 days), no MLHT was found. Thymomas/lymphosarcomas were found in one rat treated with coal dust and in two rats treated with carbon black dust (Wagner, 1976).

Groups of 16 male and 16 female Wistar-derived ICI Alderley-Park rats (Wistar derived), five to six weeks of age, received a single intrapleural injection (right axilla) of 20 mg of one of four quartz preparations (Table 25) in 0.4 ml saline. The incidence of MLHT observed in each treated group (except that receiving DQ12) over the lifespan was statistically significantly different from that in saline controls (Wagner *et al.*, 1980). [The Working Group noted that no control group receiving inert dust was reported.]

Table 25. Incidence of malignant lymphoma histiocytic type (MLHT) in rats after an intrapleural injection of 20 mg quartz

Sample	No. of particles ×10 ⁶ /μg	Size distribution (%)			Mean survival (days)	Incidence of MLHT (%)
		0-1 μm	1-2 μm	2-4.6 μm		
Min-U-Sil (93% pure)	0.59	61.4	27.9	9.1	545	11/32 (34%) ^b
D & D (pure crystalline silica; Dowson and Dobson, Johannesburg)	0.30	48.4	33.2	18.4	633	8/32 (25%) ^b
Snowit (commercial washed crystals)	1.1	81.2	12.9	5.6	653	8/32 (25%) ^b
DQ12 (standard pure quartz)	5.0	91.4	7.8	0.8	633	5/32 (16%)
Saline controls	—	—	—	—	717	0

^aFrom Wagner *et al.* (1980)

^bSignificantly different from controls by Fisher exact test, *p* < 0.05; calculated by the Working Group

Groups of 16 male and 16 female Wistar-derived ICI (Alderley Park) rats, 12 male and 12 female PVG rats and 20 male and 20 female Agus (both Medical Research Council) rats, five to six weeks of age, received a single intrapleural injection (right axilla) of 20 mg quartz as Min-U-Sil (<5 μm, the same as described in Table 25) in 0.4 ml saline and were observed for the duration of their lifespan. Groups of 16 male and 16 female Wistar rats, 12 male and 12 Agus rats and eight male and four female PVG rats were injected with saline alone. MLHT was seen in 11/32 (34%) Wistar-derived ICI, 2/24 (8.3%) PVG and 2/40 (5%) Agus

animals. Mean survival times were 545 days for Wistar rats, 666 days for PVG rats and 647 days for Agus rats. Tumour morphology was similar in all strains, except that the Wistar rats showed histological evidence of tumour spread below the diaphragm. No MLHT was found in any saline-injected control group (Wagner *et al.*, 1980). [Marked differences have been reported in two Wistar substrains: 50/60 Harwell substrain rats developed MLHT tumours compared to 0/48 Oxford colony rats. It was further shown that these tumours were derived from macrophages [treatments unspecified] (Harvey *et al.*, 1986).]

A group of 16 male and 16 female caesarean-derived SPF inbred Wistar rats, six weeks of age, received a single intrapleural administration (right axilla) of 20 mg cristobalite (prepared by heating Loch Aline sand from Safety in Mines Research Establishment, Sheffield, UK, for 1 h at 1620°C; containing 0.6×10^6 particles/ μg ; particle size distribution: 58.7% 0-1 μm , 28.9% 1-2 μm , 10.4% 2-4.6 μm ; Wagner *et al.*, 1980) in 0.4 ml saline. The animals were killed when moribund; mean survival time was 714 days. Eighteen of 32 rats developed malignant lymphoma (13 MLHT and five thymoma/lymphosarcoma). In 15 controls treated with saline only (mean survival, 720 days), no MLHT but one thymoma/-lymphosarcoma was found. In 16 rats receiving respirable size coal dust in saline (mean survival, 690 days) and in rats treated with carbon black dust (mean survival, 618 days), no MLHT was found; thymomas/lymphosarcomas were found in one rat treated with coal dust and in two rats treated with carbon black dust (Wagner, 1976).

A group of 16 male and 16 female Wistar-derived ICI Alderley-Park rats, five to six weeks of age, received a single intrapleural administration (right axilla) of 20 mg cristobalite (containing 0.6×10^6 particles/ μg ; particle size distribution: 58.7% 0-1 μm ; 28.9% 1-2 μm ; 10.4% 2-4.6 μm . Mean survival was 597 days. Of 32 rats observed for their lifespan, four developed MLHT; no such tumour was found in 16 male and 16 female saline controls (mean survival, 717 days) (Wagner *et al.*, 1980).

A group of 16 male and 16 female Wistar-derived ICI Alderley-Park rats, five to six weeks of age, received a single intrapleural injection (right axilla) of 20 mg tridymite (obtained by dissolving impurities from silica cement which had had long service at approximately 1380°C in a gas-retort house; the sample contained 0.35×10^6 particles/ μg ; particle size distribution: 34.9% 0-1 μm , 44.9% 1-2 μm , 21.2% 2-4.6 μm ; from Safety in Mines Research Establishment, Sheffield, UK). Mean survival was 525 days. Of 32 rats observed for lifespan, 16 developed MLHT. No such tumour was found in 16 male and 16 female saline controls (mean survival, 717 days) (Wagner *et al.*, 1980).

(e) *Intraperitoneal administration*

Rat: Two groups of 16 male and 16 female caesarean-derived SPF inbred Wistar rats, aged six to eight and eight to 12 months, respectively, received a single intraperitoneal injection of 20 mg quartz as Min-U-Sil (99% pure) in 0.4 ml saline. Groups of eight and 12 controls [sex unspecified] received saline only. Animals were killed when moribund; mean survival of treated animals was 462 days, and that of controls was 332 days. A total of 9/64 rats developed malignant lymphomas, two of which were MLHT and seven of the thymoma/lymphosarcoma type. None of the saline controls developed MLHT, but one developed a thymoma/lymphosarcoma (Wagner, 1976).

(f) *Intravenous administration*

Mouse: A group of 25 male and 25 female strain A mice, two to three months of age, received a single intravenous injection in the tail vein of 1 mg quartz (from the Geological Museum, Harvard University, Boston, MA, USA; average particle size, 1.6 μm) in 0.1 ml saline. A group of 75 untreated animals served as controls. Eleven quartz-treated mice were sacrificed at three months, ten at 4.5 months and 20 at six months; the numbers of controls sacrificed at these times were 25, 25 and 22, respectively. No significant difference in the presence or multiplicity of pulmonary adenomas was found between treated and control groups (Shimkin & Leiter, 1940).

Rat: A group of 16 male and 16 female caesarean-derived SPF inbred Wistar rats, six weeks of age, received a single intravenous injection in the external jugular vein of 20 mg quartz as Min-U-Sil (99% pure) in 0.4 ml saline. Mean survival time was 631 days. Of the 20 rats that survived the treatment, four developed thymomas/lymphosarcomas (Wagner, 1976). [The Working Group noted that no vehicle control was included.]

(g) *Administration with known carcinogens*

Intratracheal administration: Four groups of white rats, weighing approximately 100 g, were given the following treatments by intratracheal instillation: Group 1 (28 males and 30 females) received a single instillation of 50 mg quartz (particle size, 82% $<2 \mu\text{m}$) and 5 mg benzo[a]pyrene suspended in saline [volume unspecified]; Group 2 (37 males and 33 females) received a single instillation of 50 mg quartz followed four months later by a single instillation of 5 mg benzo[a]pyrene; Group 3 (ten males and 18 females) received a single instillation of 5 mg benzo[a]pyrene; and Group 4 (39 males and 30 females) received no treatment. The animals were observed until death and were necropsied. Lung tumours were observed in 3/11 males and 11/20 females in Group 1 that survived seven months or more (three papillomas in females; all other tumours were squamous-cell carcinomas); in 4/11 males and 0/7 females in Group 2 that survived 11.5 months or more (two papillomas and two squamous-cell carcinomas); in 0/8 males and 0/11 females in Group 3 that survived nine months or more; and in 0/16 males and 0/29 females in Group 4 that survived 16 months or more. The incidences of tumours at other sites were not related to treatment (Pylev, 1980). [The Working Group noted the absence of control groups receiving quartz without benzo[a]pyrene.]

Groups of 50 male outbred Syrian golden hamsters, seven to nine weeks of age, received weekly intratracheal administrations of 3 mg benzo[a]pyrene alone or with 0.7 mg Min-U-Sil, with 1.1 mg Sil-Co-Sil, with 3 mg ferric oxide, or with 0.7 mg Min-U-Sil plus 0.3 mg ferric oxide, in 0.2 ml saline for 15 weeks. Survivors were killed 92 weeks after the first treatment. The incidences of respiratory-tract tumours are shown in Table 26. The mean latency of the respiratory-tract tumours in all treated groups was not significantly different from that in controls. Results obtained in animals treated with quartz only are discussed above (p. 75) (Niemeier *et al.*, 1986).

Intrapleural administration: Eighty male SPF Sprague-Dawley rats, three months of age, were exposed by inhalation to ^{222}Ra at 100% equilibrium with radon daughters for 10 h

Table 26. Incidences of respiratory tract tumours in hamsters after intratracheal administration^a

Treatment ^b	Number of animals	Respiratory tumour-bearing animals	No. of respiratory tumours by site			Mean latency (weeks)
			Larynx	Trachea	Bronchi and lung	
Saline control	48	0	0	0	0	—
Saline + BP	47	22	5	3	32	72.6
Ferric oxide	50	1	1	0	0	62
Ferric oxide + BP	48	35	5	6	69	70.2
Sil-Co-Sil	50	0	0	0	0	—
Sil-Co-Sil + BP	50	36	13	13	72	66.5
Min-U-Sil	50	1	0	0	1	68
Min-U-Sil + BP	50	44	10	2	111	68.5
Min-U-Sil + ferric oxide	49	0	0	0	0	—
Min-U-Sil + ferric oxide + BP	50	38	10	4	81	66.7

^aFrom Niemeier *et al.* (1986); tumours include polyp, squamous cell-carcinoma, carcinoma and adenocarcinoma

^bBP, benzo[a]pyrene

per day on four days per week for ten weeks (total exposure equivalent to 6000 working-level months). A group of 60 rats received no further treatment. Two weeks after exposure to radon, two groups of ten rats each received a single intrapleural injection of 2 mg of either DQ12 quartz (particle size, 90% <0.5 µm) or BRGM quartz (from Fontainebleau; prepared by Bureau de Recherches Géologiques et Minières, Orléans, France; particle size, 90% <4 µm) in 0.5 ml saline. The animals were observed for lifespan, and all were necropsied. Mean survival times were 624, 665 and 723 days, respectively. Of the group exposed only to radon by inhalation, 17/60 developed bronchopulmonary carcinoma (28%) and 0/60 pleural or combined pulmonary-pleural tumours. In the group receiving radon plus DQ12 quartz, 4/10 developed bronchopulmonary carcinomas and 2/10 combined pulmonary-pleural tumours. In the group receiving radon plus BRGM quartz, 1/10 developed a bronchopulmonary carcinoma and 3/10 pulmonary-pleural tumours (Bignon *et al.*, 1983). [The Working Group noted that groups receiving quartz alone or vehicle alone were not included and that the groups receiving combined treatment were comprised of small numbers of animals.]

Intravenous administration: A group of 20 strain A mice received a single intravenous injection of 0.1 mg 20-methylcholanthrene dispersed in 0.25 ml horse serum saturated with cholesterol one week after intravenous injection into the tail vein of 1 mg quartz (from the Geological Museum of Harvard University, Boston, MA, USA; average particle size, 1.6 µm); 30 mice received 20-methylcholanthrene only. Sacrifice of half of the animals at three and 4.5 months showed no significant effect of the quartz pretreatment on the induction of pulmonary adenomas by 20-methylcholanthrene. Results obtained in animals treated with quartz only are reported above (p. 79) (Shimkin & Leiter, 1940).

Amorphous silica

(a) Oral administration

Rat: A group of 30 weanling Sprague-Dawley rats [sex unspecified] was fed 20 mg per day of a commercial sample of diatomaceous earth (from Johns Manville Co., Denver, CO, USA) [particle size not stated] mixed with cottage cheese to a concentration of 5 mg/g cheese, in addition to basal diet and filtered water *ad libitum*. The animals were observed for lifespan (mean survival, 840 days after the start of treatment). Five malignant tumours (one salivary-gland carcinoma, one skin carcinoma, two sarcomas of the uterus, one peritoneal mesothelioma) and 13 benign tumours (nine mammary fibroadenomas, one adrenal pheochromocytoma and three pancreatic adenomas) were observed in treated animals. A group of 27 controls fed commercial rat chow (mean survival, 690 days) had three carcinomas (one each in the lung, forestomach and ovary) and five mammary fibroadenomas (Hilding *et al.*, 1981).

(b) Inhalation exposure

Mouse: Groups of 75 mice (mixed strain, Medical Research Council farm) divided approximately equally by sex, about three months of age, were exposed to about 0.5 g per day precipitated silica (particle size: 'many appeared to be about 5 µm or less in diameter'), ferric oxide dust or a 1:1 mixture of the two dusts [amount unknown] in an inhalation chamber (600-l capacity) once an hour for 6 h on five days per week for one year and observed for lifespan. Groups of 75 controls of both sexes were used; survival at 600 days was 17/75 in the control group for silica and 13/73 in that for ferric oxide or the mixture. Survival at 600 days in the silica-treated group was 12/74; in the ferric oxide-treated group, 19/75; and in the silica plus ferric oxide-treated group, 18/74. The incidences of pulmonary tumours (adenomas and adenocarcinomas) in mice surviving 200 days or more were 5/63 and 5/52 in the control groups, 13/61 (21.3%) for silica alone, 17/52 (32.7%) for ferric oxide alone and 12/62 (19.3%) for silica plus ferric oxide (Campbell, 1940). [The Working Group noted the inadequate description of the exposures.]

(c) Intratracheal administration

Hamster: A group of 24 male and 24 female Syrian golden hamsters, six to seven weeks of age, received weekly intratracheal instillations of 3 mg silica [the nature of the sample was not described, except that it was obtained from Sigma Chemical Co., St Louis, MO, USA; the company's catalogues first described the item as amorphous silica and subsequently as a mixture of amorphous and crystalline particles, particle size unspecified] in 0.2 ml saline for 20 weeks and were maintained for the duration of their lifespan. A control group of 24 males and 24 females received saline alone. All animals were dead by 80 weeks. No respiratory-tract tumour was observed (Stenbäck & Rowland, 1979). [The Working Group noted the limited length of the survival period.]

(d) Subcutaneous administration

Mouse: A group of 36 female Marsh strain mice, three months old, received a subcutaneous injection of 20 mg diatomaceous earth (uncalcined, commercial diatomite

mineral filler obtained from the diatomite deposit in Lompoc, CA, USA, marketed as Celite; water content, 5.1%; particle size, 3-9 µm, with some larger particles) suspended as a 10% slurry in isotonic saline. A group of 36 female litter-mate controls received an injection of 0.2 ml saline only. The numbers of mice still alive at 19 months were 19/36 in the treated group and 20/36 in the control group. No malignant tumour was observed at the injection site in either group. The treated group showed an extensive granulomatous and fibrotic reaction (Bryson & Bischoff, 1967).

(e) *Intraperitoneal administration*

Mouse: A group of 29 female Marsh strain mice, three months old, received an intraperitoneal injection of 20 mg diatomaceous earth (as used in the above study) suspended as a 10% slurry in isotonic saline. A group of 32 female litter-mate controls received an injection of 0.2 ml saline only. The numbers of mice still alive at 19 months were 11/29 in the treated group and 19/32 in the control group. Lymphosarcomas in the abdominal cavity were reported in 6/17 treated animals and 1/20 controls ($p = 0.02$) (Bryson & Bischoff, 1967).

(f) *Intrapleural administration*

Rat: Groups of 24 female SPF Osborne-Mendel rats, 11-16 weeks of age, received an intrapleural implantation, through thoracotomy, of a coarse fibrous glass pledge on one side of which were spread 1.5 ml of 10% gelatin containing 40 mg of either Cab-O-Sil (prepared by flame hydrolysis of silicon tetrachloride; particle size, 0.005-0.015 µm; 99.9% pure) or silica soot (prepared by flame hydrolysis of silicon tetrachloride; particle size 0.05-0.15 µm; 99.9% pure). A group of 58 controls received the gelatin-covered pledge alone. Rats were observed for two years, and terminal sacrifice was performed during the 25th month. In the Cab-O-Sil-treated group, 1/18 rats surviving one year or more developed a mesothelioma; no respiratory-tract tumour was observed in the 24 silica soot-treated survivors or in the controls (Stanton & Wrench, 1972).

(g) *Administration with known carcinogens*

Intratracheal administration: Groups of 24 male and 24 female Syrian golden hamsters, six to seven weeks of age, received weekly intratracheal instillations of 0.2 ml saline; 3.0 mg silica [the nature of the sample was not described, except that it was obtained from Sigma Chemical Co., St Louis, MO, USA; the company's catalogues first described the item as amorphous silica and subsequently as a mixture of amorphous and crystalline particles, particle size unspecified] in 0.2 ml saline; 3.0 mg benzo[a]pyrene (ground for 24 h in a mullite mortar; particle size: 100% <20 µm, 98% <10 µm, 79% <5 µm, 5% <1 µm) in 0.2 ml saline; a mixture of 3.0 mg silica and 3.0 mg benzo[a]pyrene (prepared by ball-milling the suspensions together for seven days; particle size of the mixed dust: 100% <30 µm, 98% <20 µm, 80% <10 µm, 43% <5 µm, 3% <1 µm) in 0.2 ml saline for 20 weeks. Animals were observed for the duration of their lifespan. Survival at 50 weeks was 18/48 saline controls, 13/48 silica-, 15/46 benzo[a]pyrene- and 19/48 silica plus benzo[a]pyrene-treated animals. The incidences of respiratory-tract tumours were 0/48, 0/48, 5/46 (one papilloma and one

squamous-cell carcinoma of the larynx, four papillomas of the trachea) and 21/48 (eight papillomas of the trachea, one squamous-cell carcinoma of the larynx, two of the trachea, three of the bronchi/lung, three adenocarcinomas and six adenomas of the bronchi/lung) [$p < 0.001$ as compared to benzo[a]pyrene alone], respectively (Stenbäck & Rowland, 1979). The authors later reported that these effects were similar to those observed with other dusts, such as ferric oxide and titanium dioxide, mixed with benzo[a]pyrene (Stenbäck *et al.*, 1986).

Mixed dusts

Inhalation exposure

Rat: A group of female SPF Sprague-Dawley rats [initial number unspecified] was exposed by inhalation to a concentration of 200 mg/m³ of a coal-quartz dust mixture (about 10% quartz) in air for 5 h per day on five days per week every second week for 12, 18 and 24 months. After exposure for 18 and 24 months, 28/97 (29%) of animals had pulmonary tumours and 32/72 (44%) had histologically confirmed tumours (epidermoid tumours and adenocarcinomas). Of a group of control rats exposed to coal dust only, 4/36 (11%) had histologically confirmed tumours (epidermoid tumours and adenocarcinomas). In 485 unexposed controls, no pulmonary tumour was observed grossly [only six rats were examined histologically]. After 18 months' exposure, the coal-quartz dust-treated group had a more severe fibrotic reaction in the lungs than the group treated with coal dust alone (Martin *et al.*, 1977). [The Working Group noted the absence of a group exposed to quartz alone, the lack of characterization of the quartz sample and the small number of animals examined histologically.]

[The Working Group was aware of studies in rats and hamsters by inhalation exposure and intratracheal administration in which raw or spent shale dusts containing 8-12% silica were tested (Holland *et al.*, 1983, 1986). Many of these studies were evaluated in Volume 35 of the *IARC Monographs* (IARC, 1985), in the monograph on shale oils, and these data are not considered here.]

3.2 Other relevant biological data

(a) *Experimental systems*

Toxic effects

(i) *Acute toxicity*

The intravenous LD₅₀ of amorphous silica (particle size: 0.025-0.050 µm) in rats was 15 mg/kg bw and that of quartz (100-200 µm), 500 mg/kg bw (Arienzo & Bresciano, 1968).

In general, it is finely divided colloidal particles of silica in the size range of 0.002 µm that are toxic, but some toxicity is found with larger particles if the dose is sufficiently high. Doses of 1-2 mg colloidal silica or 25 mg crystalline quartz were lethal to mice following their intravenous injection (Dale & King, 1953). Intravenous injection of 1-2 mg colloidal silica was fatal to mice within minutes; doses of 30-70 mg killed rabbits, although daily doses

of 10 mg were tolerated. [Approximate particle size, presumably 0.002 µm, based on preparation techniques.] Death was concluded to be due to intravenous clotting resulting from damage to the vascular endothelium (Gye & Purdy, 1922a,b). The lethal dose in cats following intravenous injection of colloidal silica ranged from 15 to 193 mg/kg bw (Modell & Salzman, 1941).

Intraperitoneal injections of 1-2 and 30 mg colloidal silica were fatal to mice and guinea-pigs, respectively (Gye & Purdy, 1922a). Larger amorphous silica particles also kill: 30% of rats given 100 mg amorphous silica (particle size, 30% < 0.02 µm) by intraperitoneal injection died, although a 50-mg dose was tolerated (Policard & Collet, 1954).

Eleven of 12 rats died following intratracheal injection of 50 mg colloidal silica (particle size, 0.002 µm) (King, 1947). Inhaled amorphous silica (mean particle size, 0.02 µm) caused rapid death in rabbits exposed to 300 mg/m³, but 100 mg/m³ were better tolerated (Schepers, 1959).

(ii) Long-term toxicity

(1) Fibrosis

Silica

In rats exposed to quartz dust (particle size, 40% < 0.5 µm) at a level of 30 000 particles/ml for 18 h per day, five days per week, for up to 420 days, silicotic nodules, showing only reticulin fibrosis, had developed by 220 days; by 300 days, dense, rounded, fully collagenous nodules were present (King *et al.*, 1950). Similar findings have been obtained in rats (Marenghi & Rota, 1953; Watanabe, 1956; Levis *et al.*, 1958; Heppleston, 1963), guinea-pigs (Gardner, 1935), rabbits (Denny *et al.*, 1939) and monkeys (Cauer & Neymann, 1953), after periods of exposure by inhalation varying from one week to two years.

Silicotic nodules also develop following intratracheal injection of quartz. Rats given a single 50-mg injection developed reticulinized fibrotic nodules in lung tissue by 60 days and fully collagenized nodules after 120 days (King *et al.*, 1953a). Similar results have been found with various samples of quartz (Zaidi *et al.*, 1956; Saffiotti *et al.*, 1960; Saffiotti, 1962; Le Bouffant *et al.*, 1977, 1979; Reiser *et al.*, 1982). Similar lesions have been found in mice (Sahu *et al.*, 1975), guinea-pigs (Kaw & Zaidi, 1969), rabbits (Naeslund, 1939) and dogs (Mosinger *et al.*, 1961). It was found in these studies that silicotic nodules are larger and more likely to coalesce and to involve large areas of lung tissue after intratracheal injection than after dust inhalation.

Lesions other than the typical silicotic nodules have also been reported. SPF rats exposed by inhalation to 40 mg/m³ of 98.7% pure quartz dust (<3 µm) for 12 weeks developed alveolar lipoproteinosis without fibrotic silicotic nodules. Large areas of alveolar lung tissue were filled with eosinophilic granular material which gave a positive periodic acid Schiff (PAS) reaction; birefringent particles were present as well as foamy macrophages containing PAS-positive material and sudanophilic fat (Heppleston, 1967; Heppleston *et al.*, 1970). Other studies have confirmed these findings in rats and indicated

that this type of lesion is very similar to the alveolar proteinosis found in acute silicosis in humans (Gross & deTreville, 1968a,b; Corrin & King, 1970). Guinea-pigs and hamsters exposed similarly developed extensive desquamative pneumonitis and some lipoproteinosis (Gross & deTreville, 1968a,b; Corrin & King, 1970). The lipoproteinaceous material appears to be produced by hyperactive type II pneumocytes and may be related to pulmonary surfactant (Corrin & King, 1970; Heppleston *et al.*, 1974; McDermott *et al.*, 1977).

Not all forms of silica are equally pathogenic. In general, the relatively insoluble forms of amorphous silica can be fibrogenic but are less so than pure crystalline samples. Both fused (amorphous) and unfused (crystalline) silica produced nodules in rabbits following intraperitoneal injection of 200 mg dust, but the nodules produced by crystalline quartz were larger at three months; this difference became more marked with time (Silverman & Moritz, 1950). In rabbits, inhalation of 40 mg/ml amorphous silica for up to 1100 days caused only diffuse tissue reaction (Gärtner, 1952); however, intratracheal injection of amorphous silica (particles, $<1\text{ }\mu\text{m}$) produced lesions on the lymph nodes in rats six months after injection, which were described as identical to those produced by quartz dust (Osanai, 1957). Similarly, typical silicotic lesions have been produced in rats by intraperitoneal injection of 50 mg amorphous silica (Policard & Collet, 1957). Following exposure of rats by intraperitoneal injection, intratracheal injection or inhalation to a variety of silica preparations, it was reported that solutions of silicic acid and silica gels were nontoxic and nonfibrogenic, that colloidal amorphous silica was toxic but not fibrogenic, and that crystalline quartz produced a maximal fibrotic response (Klosterkötter & Jötten, 1953). The effects of samples of silica that were either completely amorphous or had a low content of crystalline material have been examined in rats, guinea-pigs, rabbits and monkeys by a number of workers (Beintker, 1943; Schepers *et al.*, 1957a,b,c; Tebbens & Beard, 1957; Furuya, 1958; Byers & Gage, 1961; Swensson, 1967; Belobragina & Elnichnykh, 1972; Podgaiko *et al.*, 1980; Groth *et al.*, 1981; Schepers, 1981; Weller, 1981; Pratt, 1983; Wózniak, 1983).

While there are differences between the pathogenic effects of crystalline and amorphous silica, differences are also seen between the individual crystalline varieties. Following intratracheal injection of 50 mg of different silica dusts into rats, tridymite was the most fibrogenic, followed by cristobalite and then quartz. Tridymite-induced nodules reached the maximal grade of fibrosis by 60 days, while those induced by quartz took 240 days (King *et al.*, 1953a). Similar findings have been obtained by Schmidt and Lüchtrath (1955), Saffiotti *et al.* (1960) and Saffiotti (1962). However, following intratracheal injection of 30 mg of different dusts to rats, stishovite was inactive while coesite and quartz were fibrogenic (with approximately the same fibrogenic potential) (Brieger & Gross, 1966, 1967). At dose levels of calcined diatomaceous earth (cristobalite content, 61%) close to the 'normal hygienic standards for humans', relatively little pathological change was found in the lungs of dogs, guinea-pigs or rats exposed by inhalation (Wagner *et al.*, 1968).

The pathogenicity of silica dusts depends on particle size. Following intravenous administration to rabbits of two quartz preparations (total injected dose, 1.3 g given as repeated injections over a period of four months), 1-3- μm particles caused more liver fibrosis over a period of two to three years than did 6-12- μm particles (Gardner &

Cummings, 1933). The pathogenicity of quartz to rabbit liver (two intravenous injections of 200 mg) increased as the particle size was reduced from 3.3 to 0.6 μm (Tebbens *et al.*, 1945). This result has been confirmed in mice by intravenous injection and in rats by intracheal and intraperitoneal administration (Swensson *et al.*, 1956). When equal mass doses are injected, a lower particle size results in an increase in the number of particles and in the surface area. However, following intratracheal injection into rats of quartz preparations with a constant surface area, maximal pulmonary fibrosis was still observed with particles 1-2 μm in diameter (King *et al.*, 1953b). Similar results were found following intratracheal injection into rats; but, following intravenous injection into mice, liver fibrosis was obtained with quartz particles 0.2-2 μm in diameter (Zaidi *et al.*, 1956). The most fibrogenic size of quartz dust particles in lung tissue is apparently 1-2 μm (King & Nagelschmidt, 1960; Goldstein & Webster, 1966).

The presence of a highly soluble amorphous surface layer on quartz particles considerably reduces their toxicity; removal of this layer with hydrofluoric acid markedly increases both the biological activity of quartz particles and the ensuing cellular reactions (Englebrecht *et al.*, 1958; Saffiotti, 1962).

Mixed dusts

The development of silicotic lesions after exposure to mixed dusts depends to some extent on the ability of silica particles to retain their toxicity in the presence of other minerals. Rabbits exposed by inhalation to quartz to which 1% metallic aluminium had been added developed no fibrosis, although pure quartz produced typical silicotic lesions (Denny *et al.*, 1939). Similarly, 1% alumina delayed fibrosis caused by silica by at least four months in intratracheal studies in rats, although 0.1% aluminium had no effect (King *et al.*, 1953c). In another study, 2% metallic aluminium failed to inhibit fibrosis following intratracheal administration of quartz to rats (Belt & King, 1943). It has been suggested that hydrated aluminium is the most effective compound in reducing the fibrogenic properties of quartz (Gardner *et al.*, 1944), although both colloidal aluminium hydroxide and powdered aluminium hydrate were found to be equally effective in rats, guinea-pigs and rabbits (Dworski, 1955). When rats were treated by inhalation with a mixture of coal and quartz dust (40% quartz), the presence of aluminium chloride reduced the severity of the pneumoconiotic lesions (Ulmer, 1964).

The pathogenicity of coal-mine dust does not correspond closely to quartz content. Studies in rats by inhalation and intratracheal injection demonstrated that other minerals present in some mine dusts reduce the pathogenic effect of quartz. This protective effect appears to be due mainly to clay minerals, illite being particularly effective although kaolin had no effect. The protective effect may be due in part to release of aluminium by clays, but effects of other minerals have not been examined (Le Bouffant *et al.*, 1982). Studies in rats, mice and guinea-pigs by various routes of administration demonstrate that iron can protect against quartz toxicity (Kettle, 1932; Gross *et al.*, 1960), as can some organic polymers (Schlipkötter & Beck, 1965; Hennies *et al.*, 1967).

Modifying effects of pulmonary infections

Pulmonary infection may exacerbate the effects of inhaled silica. SPF rats developed

only small pulmonary lesions in response to inhaled tridymite, while animals maintained under non-SPF conditions developed large and sometimes confluent nodules (Chiappino & Vigliani, 1982). It has been suggested that inhalation of quartz into the clean lungs of SPF rats leads to alveolar lipoproteinosis, while the presence of a more prolific bacterial flora in non-SPF animals predisposes to the formation of silicotic nodules (Heppleston *et al.*, 1974; Chiappino & Vigliani, 1982). [It is possible that both the presence of low-grade infection and the inhalation of extremely toxic quartz dust are involved in the development of lipoproteinosis.]

Tuberculosis has been shown to develop more easily in silicotic nodules than in normal lung tissue of animals (Gye & Kettle, 1922; Kettle, 1924). Comparison of a variety of dust samples showed that silica was the most effective in stimulating the growth of tubercular organisms (Vorwald & Landau, 1937). Following the inhalation of quartz by guinea-pigs, healing tubercles were reactivated by dust localized in the immediate vicinity of the tubercular foci; combined tubercular infection and silicosis produced more fibrosis than either agent alone (Gardner, 1930) and a nodular fibrosis similar to human silicosis (Policard & Dufourt, 1937). Other studies in rats and guinea-pigs have shown that silica dust also exacerbates infection with *Mycobacterium tuberculosis*, often producing rapidly fatal disease (review by de Balsac *et al.*, 1940; Vorwald *et al.*, 1950; King *et al.*, 1953d; Schepers *et al.*, 1957d; Gross *et al.*, 1959).

There is evidence that quartz dust increases susceptibility to protozoa (Trischmann *et al.*, 1978), bacteria (Friedman & Moon, 1977; Takeya *et al.*, 1977; O'Brien *et al.*, 1979) and viruses (Morahan *et al.*, 1977), possibly by its effect on macrophages.

(2) Effects on the immune system

Some type of immunological reaction may be involved in the tissue response to silica (Vigliani *et al.*, 1950), as indicated by the presence of autoantibodies (γ -euglobulin) in silicotic patients. It was suggested that antibodies are formed when proteins are modified by contact with quartz (Kálmán, 1957); however, when serum γ -globulins were adsorbed onto quartz, they retained their normal antigenic properties (Pernis *et al.*, 1959). Large amounts of γ -globulins were found in the hyaline tissue of human silicotic nodules (Pernis *et al.*, 1957), and hypersensitized rabbits treated with silica produced larger and more clearly demarcated collagenous lesions than controls (Powell & Gough, 1959). Attempts to demonstrate specific antibodies during the development of experimental silicosis have produced conflicting results (Antweiler & Hirsch, 1956).

The immunological phenomena involved in silicosis may be due to factors, such as interleukin 1 (Pernis & Vigliani, 1982; Schmidt *et al.*, 1982), released from macrophages that have phagocytosed dust particles. Such factors can stimulate thymocyte proliferation: following treatment of rodents with quartz, the proliferation of thymus-derived cells (T lymphocytes) in the spleen has been reported (Miller & Zarkower, 1974; Pernis & Vigliani, 1982; Hannant *et al.*, 1985). Plasma cells, mast cells and granulocytes have also been found to be involved in the reaction to silica (Saffiotti *et al.*, 1960; Saffiotti, 1962). In contrast, proliferation of splenocytes (B lymphocytes) is depressed (Miller & Zarkower, 1974, 1976), although antibody production in general has been shown in mice to be

stimulated by quartz (Mancino & Bevilacqua, 1978; Mancino *et al.*, 1983). Mice exposed to quartz by inhalation had impaired ability to respond to inhaled *Escherichia coli* antigens (Burns *et al.*, 1980).

(3) *Other pathogenic effects*

Lesions are found in organs other than lung following injection of rabbits and rats with large doses of silica, although, in most cases, the final stage of tissue damage is the production of fibrous hyaline tissue, especially in the liver (Eger & Da Canalis, 1964). In the kidney, fibrosis of the glomerular capsule was found, and amyloidosis and hyaline change were reported in the kidney tubules (Koppenhöfer, 1936: colloidal silica; Mosinger *et al.*, 1963: crystalline silica; Eger & Da Canalis, 1964: quartz).

No pathological change was observed in rats or dogs following feeding of crystalline or amorphous silica (McClendon *et al.*, 1958; Bertke, 1964; Newberne & Wilson, 1970).

(iii) *Toxicity in vitro*

(1) *Red blood cells*

The haemolytic effect of quartz and the role of particle surface characteristics in this effect have been reviewed (Nolan *et al.*, 1981; Langer & Nolan, 1985).

Silica

The levels of haemolysis obtained with several silica varieties occurred in the order tridymite > quartz > cristobalite > vitreous silica > coesite; stishovite had little effect (Stalder & Stöber, 1965). Hefner and Gehring (1975) confirmed that quartz is haemolytic and demonstrated that its concentration effect over the range 1-15 mg/ml is more rapid than that of a series of other silicates.

Mixed dusts

Singh *et al.* (1983a,b) showed that slate dusts containing crystalline silica are haemolytic and suggested that this was due to the release of silicic acid. Studies with coal-mine dusts have shown that haemolysis does not correlate significantly with the quartz content of dust from collieries mining 'low-grade' coal but does so with that of dusts from collieries mining 'high-grade' coal (Gormley *et al.*, 1980).

(2) *Macrophages*

Silica

The toxicity of different types of silica to macrophages varies considerably depending on the origin of the cells and factors such as mineralogical type and surface properties. Pure quartz reduced the viability of rat peritoneal macrophages to a greater extent than tridymite (Katsnelson *et al.*, 1984). In contrast, both tridymite and cristobalite were reported to be roughly eight times more toxic (assessed by viability) to guinea-pig leucocyte cultures than quartz or vitreous silica (Marks *et al.*, 1956). Etching the surface of quartz dust with hydrofluoric acid was found to increase its toxicity to rabbit peritoneal macrophages (Vigliani *et al.*, 1961). Similarly, etching of tridymite, quartz and cristobalite with

SILICA

89

hydrofluoric acid increased their toxicity to guinea-pig peritoneal macrophages (as measured by lactic acid production and oxygen utilization) (Kessel *et al.*, 1963). Samples of diatomaceous earth containing mainly amorphous silica were toxic to mouse peritoneal macrophages, as measured by release of lactic acid dehydrogenase, although they were less toxic than crystalline silica (quartz or cristobalite) (Bye *et al.*, 1984).

Mixed dusts

Treatment of guinea-pig peritoneal macrophages with a series of coal-mine dust samples from the Ruhr and Saar coal fields in the Federal Republic of Germany resulted in a wide range of toxicity, which was not, however, closely related to the quartz content (Robock & Klosterkötter, 1971; Reisner & Robock, 1977). A similar lack of correlation was reported with P388D₁ cells (a permanent macrophage line) treated with dusts from UK collieries mining 'low-grade' coal (Gormley *et al.*, 1980), and with guinea-pig alveolar macrophages treated with dusts from mines in the Federal Republic of Germany (Seemayer & Manojlovic, 1980; Tilkes & Beck, 1983). German coal-mine dust with a higher quartz content and smaller particle size was more toxic to guinea-pig alveolar macrophages than dust with a lower quartz content and larger particle size (Seemayer, 1984).

Contamination of the quartz surface in mixed dust samples with other minerals can greatly influence the toxic effects of the dust. Three coal-mine dust samples with quartz contents ranging from 7 to 25% had similar effects on the viability of P388D₁ cells; however, when the dusts were 'cleaned' with sodium dithionite, samples with the highest quartz levels showed much greater in-vitro cytotoxicity than the other samples (Robertson *et al.*, 1984).

In some studies, in-vivo and in-vitro effects have been compared. The cytotoxicity of dust samples (particle size, <5 µm; quartz content, 14-36%) from three ore mines to guinea-pig peritoneal macrophages *in vitro* showed little correlation with the quartz content of the dusts or with long-term fibrogenicity in rats following intratracheal injection (David *et al.*, 1981). Similarly, the cytotoxicity of 27 European coal-mine dusts *in vitro* was not directly linked to their quartz content, although the latter was associated with the degree of pathological change in the regional lymph nodes of rats following intraperitoneal injection (Bruch *et al.*, 1983).

(3) Other cell systems

Silica

Silica (Min-U-sil, 5 µm or Aerosil A380, <1 µm) increased thymidine uptake and hydroxyproline production in primary cultures of human and rabbit lung fibroblasts over that in controls, although the effect was less marked than with asbestos (Lemaire *et al.*, 1982; Richards & Hunt, 1983). Silica was found to have little effect on the cloning efficiency of Chinese hamster V79-4 cells or on giant-cell formation in a cell line of human alveolar type II cells (A549) (Chamberlain & Brown, 1978). The effects of nonfibrous diatomaceous earth were similar to those of quartz, but a fibrous variety was cytotoxic to mouse peritoneal macrophages and V79-4 cells (Chamberlain *et al.*, 1982). Quartz (DQ12) did not modify cell growth in primary cultures of rat pleural mesothelial cells (Jaurand *et al.*, 1983).

(4) *Fibroblast stimulation*

Silica

Macrophages damaged by quartz liberate specific factors that may be involved in fibrogenesis; extracts of macrophages that had been incubated with quartz stimulated an increase in collagen production by rat fibroblast cultures (Heppleston & Styles, 1967). Fibrogenesis caused by silica particles has been studied in several related in-vitro systems using alveolar or peritoneal macrophages from various rodent species (Burrell & Anderson, 1973; Harrington *et al.*, 1973; Kilroe-Smith *et al.*, 1973; Calderon *et al.*, 1974; Aalto *et al.*, 1976, 1982; Brown & Gormley, 1983; Lugano *et al.*, 1984). It has been suggested that one of the fibrogenic factors is identical to interleukin 1 (Schmidt *et al.*, 1984).

Mixed dusts

The production of fibrogenic factor(s) by rat peritoneal macrophages treated *in vitro* with a series of European coal-mine dusts and artificial mixtures of coal with known amounts of quartz was unrelated to quartz content (Heppleston *et al.*, 1984).

Effects on reproduction and prenatal toxicity

Injection of 0.0082-0.82 mg colloidal silica (Ludox) into the amniotic cavity of five-day-old chick embryos produced significant developmental defects, such as axial distortion, limb distortion and fusion of limb appendages to the body wall. Similar numbers of defects were produced by suspensions of very finely divided carbon or colloidal alumina (Williamson *et al.*, 1963); it was concluded that the effect was due to the colloidal nature of the test materials rather than to their chemical type (Williamson *et al.*, 1967).

The teratogenic effects of the carrier material of sugar-coated pills (containing 5.5% amorphous silica, Aerosil, by weight as well as a number of other substances) was examined following ingestion by pregnant rabbits. Some increase in developmental abnormalities was reported when the material was administered 70 h after coitus, but the numbers were not significantly different from those in controls (Gottschewski, 1967).

Deposition, clearance, retention, absorption and excretion

(i) *Deposition and early stages of clearance*

Following exposure of rats to 4.2 mg/m³ Belgian glass sand (particle size, 0.5-5 µm) by inhalation, initial deposition was maximal in the ciliated air passages; it was also present throughout the acini, where the intensity of deposition diminished distally. The distribution of particles was not uniform between different acini, and, with time, aggregates formed, primarily in proximal alveolar ducts but also in the distal extremities (Heppleston, 1963).

In rats exposed by inhalation to 109 mg/m³ crystalline silica (α -quartz) for 3 h, particles were found deposited upon alveolar duct surfaces, primarily in those closest to the terminal bronchioles. Within 24 h, 82% of the particles had been cleared from the alveolar duct surfaces; 12 h after exposure, 72% of the macrophages in the lavage fluid contained silica, and these high levels were maintained for 24 days after exposure. Immediately and 24 h after

SILICA

91

exposure, particles were also found in alveolar type I cells; three days after exposure, some silica particles had translocated to the alveolar interstitium (Brody *et al.*, 1982, 1985).

Alveolar macrophages very rapidly phagocytosed quartz particles (1-3 μm in diameter) (Miller *et al.*, 1978). The effects of phagocytosis and cytotoxicity of silica particles on the efficiency of alveolar clearance *via* upper airways or penetration into the pulmonary interstitium are unclear (Schiller, 1961; Gross *et al.*, 1966; Kissler *et al.*, 1982).

(ii) *Long-term clearance and retention*

Long-term (1-32 weeks) pulmonary clearance of quartz and other types of dust after inhalation has been studied in rats (Klosterkötter & Bünnemann, 1961; Le Bouffant, 1961; Policard *et al.*, 1961; Klosterkötter & Einbrodt, 1967; Le Bouffant, 1971). Due to differences in experimental protocols and discrepancies between results, a systematic pattern of clearance has not been identified. However, in general, long-term pulmonary clearance was slow and biphasic, there was considerable individual variation in clearance rates, and easily soluble amorphous silica dusts of small particle size were cleared much more rapidly than quartz. In all studies, the absolute amount of dust eliminated increased with lung burden, but the efficiency of elimination was either constant (Policard *et al.*, 1961) or decreased (Klosterkötter & Bünnemann, 1961). The amounts of quartz retained in the lungs of rats after 6-h exposure were less than proportional to the exposure concentrations (Le Bouffant, 1961). One year after inhalation exposure of rats to quartz, there was a marked reduction in alveolar retention due to lesions induced by the quartz (Le Bouffant, 1971). However, guinea-pigs exposed for up to two years to concentrations of 150 mg/m³ cristobalite or 100 mg/m³ amorphous silica retained up to 68 mg cristobalite and 120 mg amorphous silica, without evidence that lung retention decreased with time (Pratt, 1983).

In two experiments in which rats were exposed by inhalation to a respirable mixture of quartz and coal dust for nine to 18 months (Ross *et al.*, 1962; Weller, 1971), ten-fold differences in retention were found (Table 27). Quartz enrichment of the lung was not observed in either experiment. Stöber *et al.* (1967) also observed that retention of quartz dust reached a plateau.

Table 27. Retention of quartz dust in lungs of rats exposed chronically by inhalation

Exposure	Concentration (mg/m ³)	Length of exposure (months)	Amount re- tained in lung (mg)	Reference
Quartz mixed with coal dust	12	10	17	Ross <i>et al.</i> (1962)
	24	10	38	
	18	9	3.6	Weller (1971)
	18	18	6.7	
Quartz	1	12	0.07	Stober <i>et al.</i> (1967)
	1	24	0.10	
	20	16	3.8	

Quartz penetrates the lymph nodes more easily than inert dust particles (Nagelschmidt *et al.*, 1957; Klosterkötter & Büinemann, 1961); however, this route is of little importance compared to bronchial clearance (Policard *et al.*, 1961).

The lung clearance of cytotoxic quartz and inert titanium dioxide has been compared. In the first phase, lasting from one to two months, quartz and titanium dioxide were cleared at the same rate (Klosterkötter & Büinemann, 1961; Le Bouffant, 1961, 1971). In the second phase, titanium dioxide was cleared more rapidly than quartz (Klosterkötter & Büinemann, 1961), negating the hypothesis (Nagelschmidt *et al.*, 1957) that toxic dust particles are cleared more efficiently.

Modification of the toxicity of quartz particles may affect their retention in and clearance from the lung. Subcutaneous injections of polyvinylpyridine-*N*-oxide reduced the retention and penetration of quartz and increased its rate of clearance in rats (Klosterkötter & Einbrodt, 1967). Similar observations have been made in sheep exposed to quartz treated with aluminium lactate (Sébastien *et al.*, 1987).

Prior exposure to silica or the existence of silicotic lesions affect the deposition and retention of other particles, such as haematite (Heppleston, 1962; Heppleston & Morris, 1965).

(iii) *Absorption and excretion*

Quartz is slightly soluble in body fluids, forming silicic acid, and is readily excreted *via* the kidneys. After respiratory exposure to silica particles, total silicon measured in urine can be attributed to particles dissolved either in the lung or in the gastrointestinal tract. The level of silicon in urine either after clearance from the lung or after ingestion is influenced by the diet (King *et al.*, 1933a). After intraperitoneal administration to guinea-pigs of 15 ml of a solution of 300 mg sodium metasilicate, siliceous deposits were found in the kidneys (Settle & Sauer, 1960).

Intragastric or intravenous administration of particulate silica to dogs led to marked increases in the levels of silicon compounds in the urine, but not in the blood (King *et al.*, 1933b). Similarly, blood concentrations were not significantly increased in dogs exposed to quartz by intratracheal injection (Mosinger *et al.*, 1961).

Mutagenicity and other short-term tests

Silica [physical form unspecified] was reported to be inactive in the *Bacillus subtilis* *rec* assay when tested at concentrations of 0.005-0.5 M (Kada *et al.*, 1980; Kanematsu *et al.*, 1980) [details not given].

Silica (Silcron G-910) [physical form not specified] was not mutagenic to *Salmonella typhimurium* TA1535, TA1537, TA1538, TA98 or TA100 or to *Escherichia coli* WP2 *uvrA* when tested at 0.3-10 000 µg/plate in the presence or absence of a metabolic activation system from Aroclor-induced rat-liver homogenate (Mortelmans & Griffin, 1981).

Concentrations of 1-15 µg/ml quartz (Min-U-Sil) did not induce sister chromatid exchanges in Chinese hamster V79-4 cells (Price-Jones *et al.*, 1980), but 20 µg/cm² Min-U-Sil induced micronuclei in Syrian hamster embryo cells (Hesterberg *et al.*, 1986).

SILICA

93

α -Quartz ($2 \mu\text{g}/\text{cm}^2$) did not induce chromosomal aberrations or aneuploidy in Syrian hamster embryo cells (Oshimura *et al.*, 1984). [The Working Group noted that higher doses were not examined.]

Concentrations of $>2 \mu\text{g}/\text{cm}^2$ Min-U-Sil and $>10 \mu\text{g}/\text{cm}^2$ α -quartz induced dose-dependent increases in the number of morphologically transformed Syrian hamster cells (Hesterberg & Barrett, 1984).

DQ12 quartz (500 mg/kg bw) did not induce micronuclei in polychromatophilic erythrocytes of mouse bone marrow (Vanchugova *et al.*, 1985).

Quartz did not inhibit junctional intercellular communication as measured by metabolic cooperation between Chinese hamster *hprt^{+/−}* cells (Chamberlain, 1983).

(b) Humans

Toxic effects

Diseases caused by exposure to silica have been reviewed (Ziskind *et al.*, 1976; Sargent & Morgan, 1980; LeRoy Lapp, 1981; Parkes, 1982; Heppleston, 1984; Landrigan *et al.*, 1986; World Health Organization, 1986).

Silicosis is a nodular pulmonary fibrosis caused by the deposition in the lungs of fine particles of crystalline silica. Because amorphous silica is less fibrogenic than crystalline silica, silicosis has rarely been observed after exposure to pure amorphous silica (Jahr, 1981). In a cross-sectional study of 428 diatomite workers exposed for five or more years and followed for 21 years, disabling pneumoconiosis was shown to be associated almost entirely with exposure to cristobalite, formed after high-temperature calcining of the diatomite (Cooper & Jacobson, 1977).

Although rapidly progressive silicosis has been described following massive exposure to silica, the typical course is years to decades long. A clear exposure-response relationship has been demonstrated between cumulative exposure to respirable silica and development of the radiographic and functional abnormalities of silicosis (Westerholm, 1980; Banks *et al.*, 1981a).

Pure silicosis is characterized pathologically by the presence of multiple fibrohyaline nodules, 2-6 mm in diameter, that form a whorled pattern (Parkes, 1982) and are distributed mostly in the upper halves of the lungs (peribronchial and periarterial region) (World Health Organization 1986). Similar lesions may be seen in the hilar lymph nodes (Sargent & Morgan, 1980; Jones, 1983). Continuous exposure to crystalline silica results in an increase in size of existing lesions and the formation of new nodules. Continued exposure may also result in massive fibrotic lesions, consisting of matted conglomerates (World Health Organization, 1986).

Silicosis can be categorized radiographically into simple silicosis (mainly small rounded parenchymal opacities) and conglomerate silicosis (large radiographic opacities of at least 1 cm in diameter) (e.g., Sargent & Morgan, 1980). Early silicosis shows small, rounded opacities of moderate radiodensity, varying from 1-3 mm in diameter (Landrigan *et al.*, 1986). Exposure to crystalline silica can result in silicosis that is not detectable radiologically

(Craighead & Vallyathan, 1980). Pleura may be thickened during the silicotic process (Parkes, 1982; World Health Organization, 1986).

Silicotic fibrosis may progress even after cessation of exposure to silica. In some patients, especially those with progressive, massive silicosis, severe respiratory insufficiency may occur, usually many years after cessation of exposure (Sargent & Morgan, 1980). Coronary insufficiency (*cor pulmonale*) often complicates advanced silicosis, but the principal cause of death in silicotics is nonmalignant respiratory disease (Westerholm, 1980; Finkelstein *et al.*, 1982; Zambon *et al.*, 1985; Kurppa *et al.*, 1986; Zambon *et al.*, 1986).

Tuberculosis frequently complicates silicosis (Snider, 1978), and the risk for tuberculosis is also increased in workers exposed to silica who have no radiographic evidence of silicosis (Sargent & Morgan, 1980). Elevated proportionate mortality ratios for tuberculosis have been found in the pottery industry (Thomas, 1982) and in the granite industry (Davis *et al.*, 1983). Pulmonary infections of many other etiologies also occur in association with silicosis (Parkes, 1982).

Mixed-dust fibrosis results from simultaneous inhalation of crystalline silica and of substantial amounts of other dusts (e.g., carbon, iron oxides, silicates); the silica content of the total dusts with this effect is usually <10%. The radiographic features of mixed-dust fibrosis differ from those of nodular silicosis, in that they are more frequently irregular (McLaughlin, 1957; Parkes, 1982).

Neither the risk of developing silicosis nor the progression of the radiographic lesions of silicosis is associated with smoking behaviour (Hughes *et al.*, 1982; Hessel & Sluis-Cremer, 1986; Landrigan *et al.*, 1986; Rice *et al.*, 1986).

In persons with coal-workers' pneumoconiosis, the risk of developing progressive massive fibrosis increases with increasing concomitant exposure to crystalline silica (Jacobsen & Maclaren, 1982).

Effects on reproduction and prenatal toxicity

No data were available to the Working Group.

Deposition, clearance, retention, absorption and excretion

(i) Deposition

The presence of free silica particles in lung parenchyma at autopsy demonstrates that a fraction of such aerosols is respirable. Deposition of airborne free silica depends mainly on particle size and increases with aerodynamic diameter above 1 µm (Raabe, 1984); total deposition of particles of 5 µm (geometrical diameter) can reach a level as high as 90% (van Wijk & Patterson, 1940). Increased tracheobronchial deposition was found in silicotic patients (Roy *et al.*, 1984) but not in coal workers with simple pneumoconiosis (Love *et al.*, 1971).

(ii) Clearance

A four-fold increase in the content of silica (measured as elemental silicon) in sputum has been found in patients with silicosis compared to controls (Sárdi & Tomcsányi, 1967);

SILICA

95

however, Roy *et al.* (1983) reported reduced tracheobronchial clearance in such patients. Tracheobronchial clearance is usually rapid and leaves the airways essentially free of particles within 24 h (Sanchis *et al.*, 1972).

Macrophages containing quartz are found in pulmonary lavage fluids from silicotic patients (Sébastien, 1982). The percentages of lavaged macrophages containing quartz particles were found to increase with duration of exposure in Vermont granite workers (Christman *et al.*, 1985).

In coal miners, the proportion of free silica in lymph nodes is much higher than that in the whole lung (Carlberg *et al.*, 1971; Chapman & Ruckley, 1985). Lymphatic dispersal of silica particles can cause silicotic lesions in such organs as liver, spleen and bone marrow (Slavin *et al.*, 1985). It is uncertain whether enhanced lymphatic clearance of quartz is related to the chemistry or size of particles, although dust in lymph nodes is generally finer than dust in lung (Ulrich & Juck, 1967).

(iii) *Retention*

Sixteen studies provide data on the mass of quartz and total dust retained in the lungs at autopsy from a total of some 1406 cases (Hale *et al.*, 1956; King *et al.*, 1956; McLaughlin & Harding, 1956; Faulds *et al.*, 1959; Watson *et al.*, 1959; Nagelschmidt, 1960; Rivers *et al.*, 1960; Faulds & Nagelschmidt, 1962; Nagelschmidt *et al.*, 1963; Rossiter *et al.*, 1967; Bergman & Casswell, 1972; Rossiter, 1972; Davis *et al.*, 1977; Dobreva *et al.*, 1977; Ruckley *et al.*, 1981; Verma *et al.*, 1982). Quartz contents were narrowly distributed over the range of 0-5 g/both lungs, contrasting with the wide distribution of total dust contents which range from 0-100 g. Maximum lung storage probably depends on several factors, including the characteristics of exposure and the nature of the dust. Apparently, lungs do not accumulate more than 5 g of quartz, even in severe silicosis (Nagelschmidt, 1965), but they can accumulate up to 100 g of carbon dust (Watson *et al.*, 1959). In coal workers, the retention efficiency was higher among cases of progressive massive fibrosis and greater for quartz than for coal (Ruckley *et al.*, 1981).

(iv) *Absorption and excretion*

Free silica particles are slightly soluble in body fluids, leading to the formation of silicic acid and colloidal suspensions (King & McGeorge, 1938). The absorption of dissolved silica is sufficient to increase its level in the blood and urine of exposed persons (King *et al.*, 1933a; Goldwater, 1936; King & McGeorge, 1938). In subjects exposed to silica dust, decreasing levels of silica were observed in blood and urine with advancing stages of silicosis (Stolman & Stewart, 1985).

Diet has a great influence on the urinary excretion of silica (King *et al.*, 1933a; Goldwater, 1936).

Mutagenicity and chromosomal effects

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity in humans

(a) Ore mining and quarrying

(i) Case reports and descriptive studies

Initial concern about pulmonary cancer arose from the observations of Paracelsus and Agricola in the 16th century that Schneeberg metal ore miners were dying of lung diseases later thought to be respiratory cancer (Hunter, 1978), of which radium ore decay products were the probable cause (Peller, 1939). Many subsequent case reports recorded the presence of lung cancer in metal miners; see, for example, Bradshaw *et al.* (1982), McGlashan *et al.* (1982) and Sluis-Cremer (1986) in southern Africa; Gylseth *et al.* (1981) in Norway; and Icsó and Szöllösová (1984) in Czechoslovakia.

An association between silica exposure and lung cancer was also suggested in analyses of data for the mining industry in the USA by Milham (1983) in Washington state (1950-1979), Petersen and Milham (1980) in California (1959-1961) and Williams *et al.* (1977a,b) from the US Third National Cancer Survey Study (1969-1971).

(ii) Epidemiological studies

A gold mine in South Dakota (USA) was the subject of three cohort studies, mainly because the host rock was cummingtonite-grunerite, an amphibole mineral, and the suspicion that dust containing cleavage fragments and fibres would carry the carcinogenic risks of amosite asbestos.

Gillam *et al.* (1976) studied a cohort (followed during 1960-1973) of 440 male miners employed underground at this mine for at least five years and who had never worked in another underground mine. A standardized mortality ratio (SMR) of 370 was calculated for respiratory system malignancies (10 observed, 2.7 expected); however, the odds ratio was greater within 20 years of first employment (5.4) than later (3.2).

McDonald *et al.* (1978) conducted a larger study of the same gold mine using a cohort comprising 1321 men with at least 21 years employment at the mine. SMRs based on South Dakota mortality rates showed considerable excess mortality from all causes (631 observed, 549.7 expected; SMR, 115); there were 37 cases of pneumoconiosis (0 expected), 39 of tuberculosis (3.6 expected) and 264 of heart disease (232.5 expected) with a corresponding deficiency for all other causes (134 observed, 160.1 expected). There was no overall excess of respiratory cancer (17 observed, 16.5 expected), although, in the first half of the follow-up period (1937-1955), six deaths from lung cancer were observed against 3.4 expected. There was one death from mediastinal mesothelioma (without autopsy) in a surface worker. Using dust exposure data from company midget impinger samples and the estimated average silica content of 39%, the authors examined the mortality risks in five categories of dustiness; they showed linear relationships for tuberculosis and pneumoconiosis (McDonald & Oakes, 1984). Using three categories of dustiness, no correlation with respiratory or gastrointestinal cancers was found (McDonald *et al.*, 1978).

Brown *et al.* (1986) later conducted a comprehensive assessment of miners at the same gold mine in South Dakota, USA. The cohort included 3328 white male miners employed

SILICA

97

for at least one year between January 1940 and December 1964 and followed up until 1 June 1977. The authors calculated SMRs against US mortality rates for white males. The SMR for malignant neoplasms of trachea, bronchus and lung was 100 and was not affected by latency, accumulated dust exposure or length of employment (there was a SMR of 500 based on only three cases for cancer of the other parts of the respiratory system). Large excesses were again observed for respiratory tuberculosis (SMR, 364) and other respiratory diseases (SMR, 279), especially for men employed before 1930 (SMR, 792 and 510, respectively).

[None of the three studies of this gold mine included data on smoking habits, and the most recent study gave measurements of arsenic made in 1977 (geometric mean, $1.17 \mu\text{g}/\text{m}^3$) and of radon daughters made in 1960-1977 (0-0.17 working levels). The Working Group considered that these measurements may not have applied to earlier periods.]

Katsnelson and Mokronosova (1979) examined mortality at a USSR gold mine, 1948-1974, and compared it with that of a nearby town (excluding those who worked with chromate dusts). Elevated relative risks for lung and stomach cancer were reported among male underground gold miners. [The Working Group noted that unconventional methods were used to calculate relative risks and that no data were available on dust exposures or on smoking.]

Armstrong *et al.* (1979) followed 1974 gold miners from Kalgoorlie, Western Australia (whose smoking habits were measured in 1960-1962), for silicosis incidence and general mortality through 1975 and compared the results with rates for Western Australia, 1963-1976. The SMR for respiratory cancer (59 observed, 40.8 expected) was 140 ($p < 0.01$), and that for pneumoconiosis (11 observed, 1.7 expected), 640. There was 40% excess lung cancer mortality in underground workers compared to surface workers, and 13% excess in silicotics (both nonsignificant). The authors noted that slightly more gold miners smoked (66%) than did Australian coal miners (59%). Environmental assessments of this mine showed low exposures to radon (up to 11 pCi/l; 0.045 working levels) and that the ore body contained arsenic at levels up to 335 mg/kg.

Muller *et al.* (1983) studied 50 201 male miners in Ontario, Canada, including 6972 underground gold miners, who had been examined 1955-1977. SMRs were calculated using appropriate age-specific mortality rates for the male population of Ontario. SMRs for cancers of the trachea, bronchus and lung cancers (196 observed, 135 expected; SMR, 145; $p < 0.001$) and for stomach cancer (60 observed, 40.4 expected; SMR, 148; $p = 0.002$) were significantly raised, as were those for silicotuberculosis and silicosis. No information on dust levels was available. [The Working Group noted that the rock in the ore body in Ontario gold mines contains 20% silica by weight; no data were available on airborne dust levels, silica levels, arsenic levels or radon daughter levels.] This study also evaluated the cancer risk for miners of other ores, including nickel, copper, iron and other or mixed ores. The latter two categories included miners, other than uranium miners, who had spent 85% or more of their total mining experience in Ontario mines other than gold, nickel-copper and iron ('other ore miners') and miners, other than uranium miners, who had worked <85% with any metal ore ('mixed-ore miners'). Among the 11 337 nickel-copper miners, the only remarkable excess was a SMR of 327 (based on three cases, nonsignificant) for nasal

cancer. The cohort of 7125 full-time underground mixed-ore miners had an overall SMR of 101 (1163 observed, 1157.1 expected) for all causes, with highly significant excesses of silicosis and chronic interstitial pneumonia (68/3.19) and silicotuberculosis (35/0.3; $p < 0.001$), and a SMR of 145 (101/69.5; $p < 0.001$) for cancer of the trachea, bronchus and lung.

Costello (1982) conducted a follow-up study of 12 258 white miners included in the 1958-1961 US Public Health Service survey of silicosis in the metal mining industry. SMRs were calculated using mortality rates for white males in the 16 states where the mines were located. The cohort had an SMR for all causes of 105.9 (1987 observed, 1876.8 expected; $p < 0.01$); for cancer of the trachea, bronchus and lung, 126.6 (163 observed, 128.8 expected; $p < 0.01$); and for pneumoconiosis (mostly silicosis), 343.6 (27 observed, 7.9 expected; $p < 0.01$). The rates for both digestive-tract cancers and hypertensive heart disease were significantly reduced. Cause-specific SMRs for cancer of the trachea, bronchus and lung were significantly raised ($p < 0.05$) in several groups of these miners: 130.0 among lead-zinc miners; 354.6 for mercury miners; and 346.5 for chrome miners. Death rates from pneumoconiosis were high in all groups. In the 1958-1961 survey, 15% of metal miners were nonsmokers, 11% were ex-smokers and 74% were current smokers (including pipe and cigar). Forced expiratory volume (1 sec):forced ventilatory capacity ratios were strong predictors of subsequent mortality from all cancers, including those of the respiratory tract.

Excesses of lung cancer have been reported in several other metal mining groups, in all of which radon daughters were a confounding factor; e.g., Swedish iron and sulphide ore miners (Larsson & Damber, 1982), British haematite miners (Boyd *et al.*, 1970), Canadian fluorspar miners (de Villiers & Windish, 1964), Swedish zinc-lead miners (Axelson & Rehn, 1971; Axelson & Sundell, 1978), and Swedish iron-ore miners (Jorgensen, 1973; St Clair Renard, 1974; Edling, 1982; Radford & St Clair Renard, 1984). [The Working Group noted that the role of silica could not be assessed in these studies.]

Higgins *et al.* (1983) examined the mortality, 1952-1976, of taconite miners in Minnesota (USA) against state mortality statistics. Overall, there were 298 deaths observed and 343.7 expected (SMR, 87); the SMR for respiratory cancer was 84 (15 observed, 18 expected), and that for digestive cancer was 114 (20 observed, 17.6 expected). Analysis of mortality more than 20 years after first employment showed five deaths from all malignant disease (5.97 expected); the corresponding figures for respiratory cancer were two observed with two expected. Cumulative dust exposure derived from total respirable and silica dust concentrations indicated no trend for respiratory or gastrointestinal cancers (cumulative silica dust exposure, none to $>1000 \text{ mg/m}^3 \times \text{years}$). The authors remarked that silica exposures were generally low. [The Working Group noted that the length of follow-up was short, and the statistical power of the study to assess cancer risk was therefore limited.]

Lawler *et al.* (1983) examined the mortality of 10 403 white male employees of a Minnesota (USA) haematite ore mining company (1937-1978) and contrasted it with that of US white males. Chemical analyses of the ore showed an average silica content of 8% in 1943 but 20-25% in the ore being mined in the late 1970s. For the total cohort (underground and above-ground miners), the SMR for all causes was 93 (4699 observed, 5059 expected). Mortality from tuberculosis (33/74.0) and respiratory disease (234/295.5) was significantly

($p < 0.01$) lower than expected; no elevated risk from these two causes of death was seen for underground miners. For stomach cancer, underground miners had a SMR of 167 (77/46.1; $p < 0.05$) and above-ground miners had an SMR of 181 (49/27.0; $p < 0.05$). For lung cancer, the SMR was 100 for underground miners and 88 for above-ground miners. Underground miners also had a SMR of 182 (9/4.9) for Hodgkin's disease. No data on smoking habits or exposure to radon daughters were obtained. [The Working Group noted that exposures in the Minnesota iron mines were complex and included fibrous amphiboles as well as silica. In addition, stomach cancer rates in Minnesota are among the highest in the USA, and no adjustment was made.]

A group of 1173 iron miners in Lorraine (France) was observed for five years following clinical examinations and lung function tests (Pham *et al.*, 1983). During this period, there were 40 deaths *versus* 39 expected on the basis of rates for the general male population of Lorraine. There were 13 deaths from lung cancer, giving a relative risk of 3.5 (95% confidence interval, 1.9-6.0). All the lung cancer cases were found among underground workers; they were all smokers, and they had had a longer mean length of employment underground (23.6 years) than the whole underground group (16.7 years). Measured levels of radon daughters were approximately 0.03 working level in the mine and 0.07 working level in the return air, considered by the authors to be too low to explain the excess. The prevalence of smoking was higher (66%) in the study population than in a general population sample (52%). [The Working Group noted that the study was carried out on 1173 persons randomly selected from among 5300 iron miners, but that the precise method of selection was not described. Further, the methods for ascertaining causes of death for cases and referents were not comparable.]

(b) Coal mining

Coal miners are typically exposed to low levels of silica. In epidemiological studies of cancer in this occupational group, the role of silica has therefore not commonly been addressed. In studies of British coal miners, no elevated risk of lung cancer has been seen (Kennaway & Kennaway, 1947; James, 1955; Stocks, 1962; Goldman, 1965; Liddell, 1973; Cochrane *et al.*, 1979; Miller & Jacobsen, 1985). In the one study in which silica exposure and cancer mortality were assessed, no association was found (Miller *et al.*, 1981; Miller & Jacobsen, 1985). Some studies of US coal workers have found elevated lung cancer risks, which may be explained by cigarette smoking (Enterline, 1964, 1972; Rockette, 1977), whereas other studies on US coal workers have not indicated an increase (Costello *et al.*, 1974; Ortmeyer *et al.*, 1974).

Several studies have evaluated the relation between coal workers' pneumoconiosis and lung cancer. Most have found no relationship (Liddell, 1961; Cochrane *et al.*, 1979; Miller & Jacobsen, 1985). An exception is the autopsy case-control study of Vallyathan *et al.* (1984), in which the authors matched for age at death, pack-years of smoking and years of underground mining. There was a significantly elevated odds ratio [not given; $p = 0.005$ for McNemar's test]: 84% of lung cancer cases had pneumoconiosis *versus* 66% among controls. [The Working Group noted that data on radon levels were not available.]

Mortality rates from stomach cancer are slightly elevated in some studies of coal miners (Stocks, 1962; Enterline, 1964; Matolo *et al.*, 1972; Rockette, 1977; Miller & Jacobsen, 1985). In the only epidemiological study that systematically assessed silica content within coal-mine dust, the risk of digestive cancers was found to be significantly related to increasing exposure to respirable coal-mine dust. The risk for the highest silica-exposure group was 1.64 times that of the lowest exposure group (statistically significant); there was no effect of silica exposure on survival (Miller *et al.*, 1981). One case-control study in the Netherlands (Swaen *et al.*, 1985) found no association between mortality rates for stomach cancer and employment as a coal miner. One 30-year prospective study of gastric cancer in South Wales found no difference between coal miners and non-coal miners (Atuhaire *et al.*, 1986).

(c) *Granite and stone industry*

(i) *Case reports and descriptive studies*

Kennaway and Kennaway (1947), in their classical analysis of occupational mortality in the 1920s and 1930s in England and Wales, observed that stonemasons and sandblasters, but not quarrymen, had consistently elevated mortality from lung cancer and that stonemasons but not quarrymen had elevated mortality from laryngeal cancer. Similar observations were made with regard to lung cancer in the USA by Milham (1983) and Dubrow and Wegman (1984). No increase in risk for stomach cancer was seen, except in the study by Milham (1983).

(ii) *Epidemiological studies*

Selikoff (1978) examined a 932-man cohort of unionized New York City tunnel workers from 1955 to 1972. There was a SMR of 495 (11 observed, 2.2 expected) for pulmonary tuberculosis, and 20 cases of pneumoconiosis/silicosis were observed. There was a SMR of 160 (21 observed, 13.2 expected) for lung cancer. The risk of respiratory cancer rose with the number of years worked: <10 years, 4/3.2; 10-19 years, 5/5.2; 20-29 years, 8/3.8; ≥30 years, 4/0.9. [The Working Group noted that no data were available on smoking histories, on dust concentrations or on exposure to radon.]

Puntoni *et al.* (1979) compared the lung cancer risk among 190 workers engaged in sandblasting ('stakers') among a cohort of 2190 shipyard workers in Genoa, Italy, with the general male population of the town. The workers had SMRs of 376 (16 observed, 4.25 expected; $p < 0.05$) for lung cancer and 504 (3 observed, 0.59 expected; $p < 0.05$) for laryngeal cancer; there were 19 observed cases of respiratory disease versus 7.2 expected ($p < 0.0005$). The authors noted that these workers were exposed to mineral oils and to asbestos, in addition to silica, but no quantitative data were provided. [The Working Group noted that no information was given on smoking histories.]

Vutuc (1983) reported an Austrian case-control study of lung cancer in which data on occupation and smoking history were collected. Of the 1580 cases, 177 had been employed in 'mining and processing of stone'. When patients in this group were compared with patients with 'white-collar' employment, the odds ratio (adjusted for age and smoking consumption)

was 2.0 ($p < 0.01$). [The Working Group considered that this result could have been due to differences in social class.]

Davis *et al.* (1983) conducted a proportionate mortality study on 969 deceased, white, male granite workers in Vermont, USA, who had died between 1952 and 1978. These men had participated in a voluntary medical surveillance programme, and their X-rays were on file at the Division of Industrial Hygiene of the Vermont Department of Health. Vermont granite contains approximately 30% crystalline silica, and stringent dust controls were introduced in this industry between 1937 and 1940. In 1970, the respirable dust to which Vermont granite workers were exposed contained 2-19% silica (Peters *et al.*, 1972). Cumulative dust exposure was assessed for study subjects, and the data were analysed after excluding cases of tuberculosis and silicosis. Slight excesses for cancers of the digestive tract (57/49.6), lung (62/52.6) and larynx (5/2.3) were reported, with a proportionate mortality ratio of 1.3 for general respiratory cancer (95% confidence interval, 1.0-1.6). The ratio for lung cancer was 1.1 for men employed before 1940 and 1.4 for those employed after 1940. No apparent trend emerged relating dust exposure categories to digestive cancer, respiratory diseases or lung cancer. [The Working Group noted that data on smoking habits were not available, and the voluntary nature of participation in the programme might have introduced 'volunteer bias'.]

Costello and Graham (1986) conducted a cohort study of 5414 Vermont granite workers from 1950 to 1982, using personnel information on file in the Occupational Hygiene Division of the Vermont State Health Department to ascertain date of hire and date of death. Preliminary results showed significant excess mortality from silicosis (SMR, 586.6) and tuberculosis (SMR, 473.8), but the excesses were confined to workers hired before 1940 for silicosis and before 1930 for tuberculosis. No increase in risk was observed for lung cancer, although there was 27% excess mortality from pulmonary cancers among workers hired before 1940. [The Working Group noted that enrolment in the cohort depended on voluntary participation in the medical surveillance programme; no information was available on smoking habits or on dust exposure; and the low SMR for deaths due to all causes suggests incomplete tracing.]

Kurppa *et al.* (1982) reported that among 1087 Finnish male granite workers employed for at least three months between 1940 and 1971 and followed until 1975 there were 15 deaths from gastrointestinal cancer (7.4 expected; SMR, 202; $p < 0.02$).

Steenland and Beaumont (1986) conducted a proportionate mortality study of 1905 white members of the US Granite Cutters Union, using US rates for comparison. Significantly excess mortality from nonmalignant respiratory disease (mostly silicosis) and from tuberculosis and silicotuberculosis was observed (proportionate mortality ratios, 4.18 and 13.56, respectively). The ratio for lung cancer (1.19; 97 observed, 81.1 expected) was not significantly elevated (95% confidence interval, 0.97-1.46); further, there was no trend in lung cancer risk over duration of exposure or calendar time. [The Working Group noted that no data on smoking habits were available.]

(d) *Ceramics, glass and related industries*

(i) *Descriptive studies*

Kennaway and Kennaway (1947) reported that potters had not only massive risks for silicosis and tuberculosis but also elevated risks for cancers of the lung and larynx. Dubrow and Wegman (1984) reported that glass workers in the age group 55-74 years had a mortality odds ratio of 3.14 (11 observed, 3.5 expected) for cancer of the trachea, bronchus and lung, after adjustment for social class.

(ii) *Epidemiological studies*

Thomas (1982) examined the mortality of male members of the US Potters and Allied Workers Union for 1955-1977. There were significantly elevated ($p < 0.01$) proportionate mortality ratios for tuberculosis (3.39; 62 observed, 18.3 expected), nonmalignant respiratory disease (frequently noted as silicosis; 1.54; 268 observed, 173.7 expected) and lung cancer (1.21; 178 observed, 146.6 expected). The lung cancer excess appeared to be localized among workers in the sanitary-ware divisions (62 observed, 34.4 expected). Silica exposure was said to be similar in sanitary-ware divisions and in other parts of the plants but to be characterized by the use of talc to dust moulds (Thomas *et al.*, 1986). [The Working Group noted that no data were available on smoking habits or on the asbestos content of the talc.]

Forastiere *et al.* (1986) examined the lung cancer risk among Italian pottery workers for 1968-1984 in a matched case-referent study, involving 72 lung cancer cases and 319 matched controls. Next-of-kin were interviewed by public health nurses who were unaware of the case/referent status of the person. Smoking habits were accounted for in the analysis. A Mantel-Haenszel rate ratio of 2.0 (95% confidence interval, 1.1-3.5) was found for employment in the ceramics industry. Ceramic workers who had been compensated for silicosis had a rate ratio of 3.9 (95% confidence interval, 1.8-8.3), while those without silicosis had a rate ratio of 1.4 (95% confidence interval, 0.7-2.8). The risk of lung cancer appeared to increase with length of employment.

Puntoni *et al.* (1985) studied a cohort of workers exposed to silica at a refractory plant in Genoa, Italy, for 1960-1979. In comparison with mortality rates for the male population of Genoa, their overall SMR was 122 (73 observed, 60 expected), and that for all tumours, 121 (23/19). There was a striking excess of nonmalignant respiratory disease (SMR, 304; 17/5.6; $p < 0.01$). The SMR for cancer of the lung, bronchus and trachea was 167 (6/3.6) for silicotics and 208 (5/2.4) for nonsilicotics. [The Working Group noted that data on smoking habits were not evaluated systematically.]

Katsnelson and Mokronosova (1979) examined mortality at two aluminosilicate fire-clay plants (1948-1970) and at a refractory silica-brick plant (1950-1970) in the USSR. The rates were compared with those in nearby towns, excluding persons who had worked with chromate dusts. Male workers at the three plants had elevated relative risks for lung cancer and for gastric cancer. [The Working Group noted that unconventional methods were used to calculate relative risks and that no data were available on dust exposures or on smoking habits.]

(e) *Diatomite industry*

No case report or epidemiological study was available to the Working Group.

(f) *Foundries and metallurgical industries*

Exposures in foundries are complex: in addition to silica, foundry workers are exposed to polycyclic aromatic compounds, aromatic amines, formaldehyde and many other compounds, some of which have been shown to be carcinogenic (IARC, 1982a,b, 1983, 1984).

Only studies in addition to those reported in the previous IARC monograph on iron and steel founding (IARC, 1984) are reported here.

(i) *Descriptive studies*

Dubrow and Wegman (1984), in a proportionate mortality study of foundry workers in Massachusetts, USA, adjusted for social class, reported that foundry workers aged 20 to 64 had a mortality odds ratio of 4.12 for cancer of the trachea, bronchus and lung.

(ii) *Epidemiological studies*

Sherson and Iversen (1986) evaluated the risks for cancer of the lung and for respiratory diseases among a cohort of 5579 Danish male foundry workers. These workers had previously been examined in national surveys from 1967-1969 and 1972-1974, and work histories and X-rays had been obtained and stored in the Danish Foundry Worker Register; however, data on smoking habits were not included. Job exposures were ranked by exposures to dust, polycyclic aromatic hydrocarbons and carbon monoxide; some jobs could not be classified. Excess numbers of deaths were observed from lung cancer (SMR, 115; 74 observed, 64.4 expected) and nonmalignant respiratory disease (SMR, 157; 66 observed, 42.0 expected; $p < 0.01$). An exposure-response gradient for lung cancer was observed for years of employment: [SMR for <25 years, 96]; SMR for >25 years, 159 ($p < 0.05$).

Fletcher (1986) reported two studies of UK foundry workers. The first was a cohort study of 11 048 male workers from ten steel foundries who began work between 1946 and 1965, worked for at least one year and were followed until 1978. Overall, there was a SMR of 149 (219 observed, 147.4 expected; $p < 0.001$) for lung cancer, a risk shared by many dusty occupations in the plants. There were three deaths from silicosis among 2016 deaths in this population. The analysis focused on a subset of the population exposed to processes that are known to generate siliceous dust, comprising sand preparers, moulders, coremakers, furnace repairmen, mould knockout men, shotblasters and dressers. The risks for nonmalignant respiratory disease (SMR, 135; 82/60.7; $p < 0.05$), lung cancer (SMR, 171; 102/59.7; $p < 0.001$) and stomach cancer (SMR, 190; $p < 0.01$) were significantly elevated; and for lung cancer and nonmalignant respiratory disease, there was a positive association with length of employment. Excluding the first ten years of follow-up, the SMR for lung cancer was 180 ($p < 0.001$); for workers who were not exposed to silica, the SMR for lung cancer was 89. There was a significant trend of declining risk of mortality from

nonmalignant respiratory disease with recency of entry into the cohort, but the risk for lung cancer showed a nonsignificant but increasing trend. [The Working Group noted that no data on smoking habits were available, although previous studies of British foundry workers showed that their smoking rates were similar to UK national rates. No data on levels of exposure to silica were available.]

Fletcher (1986) also reported a proportionate mortality study of 1540 recipients of death benefits paid to British foundry union members for 1979-1982. Four job categories — skilled moulders, semiskilled moulders, dressers and labourers — were analysed; the standardized proportionate mortality ratios for lung cancer were 125 (96 observed, 76.8 expected; $p < 0.05$), 154 (40/26; $p < 0.05$), 75 (10/13.3) and 106 (41/38.7), respectively. Among skilled moulders, mortality from lung cancer, but not from nonmalignant respiratory disease, was inversely correlated with length of union membership. There were five deaths from silicosis. [The Working Group noted that no data were available on levels of exposure to silica.]

Silverstein *et al.* (1986) reported a proportionate mortality analysis of 221 deaths between 1970-1981 among white male workers with at least ten years' cumulative employment in a US iron foundry, compared with US national rates. Dust concentrations in breathing-zone air samples during 1950-1976 were in the range of 8.8-18.8 million particles per cubic foot; the percentage of free silica ranged from 14-26% in 1970 and was 20% in 1976 (Mirel *et al.*, 1986). Smoking status (ever-smoker or nonsmoker) was established. Standardized proportionate mortality ratios for white males were 148 (28 observed, 18.9 expected) for lung cancer and 177 (25/14.1) for nonmalignant respiratory disease. The ratio for lung cancer in smokers was 159 (23/14.5) relative to that of all US males ($p < 0.05$) and 157 relative to that of US veterans who smoked [$p = 0.13$]. An excess of cancers of the haematopoietic system (198; 9/4.5; $p < 0.05$) was reported.

Kjuus *et al.* (1986) examined cancer incidence and mortality among a cohort of 6494 male workers employed in the Norwegian ferroalloy industry for more than 18 months before 1970 and followed between 1953 and 1982, who were exposed to crystalline and amorphous silica. The SMR for cancers at all sites was 94 (634 observed, 674.1 expected; 95% confidence interval, 87-102); and increased rates were observed for cancers of the colon (56/50.6) and nasosinuses (5/2.7) and malignant melanoma (18/14.6), but not for lung cancer. The overall SMR was 90 (1935/2150.3; 95% confidence interval, 86-94). Some data on smoking habits and data on total dust levels were available only for the preceding 15 years. [The Working Group noted that no data on levels of exposure to amorphous silica were provided.]

(g) *Silicotics*

(i) *Case reports and descriptive studies*

A large number of studies have been made of the occurrence of lung cancer in post-mortem series of silicotics. Comparisons of lung cancer rates in these autopsy series with those of non-silicotics have given conflicting results (e.g., Rüttner, 1970; Otto & Hinüber, 1972). The subject has been reviewed by Hueper (1966) and, more recently, Maillard (1980) and Heppleston (1985). [The Working Group noted that it is often difficult to draw

inferences from autopsy findings, due to potential selection biases of deaths that are necropsied and to the lack of an appropriate comparison group.]

Roadhouse Gloyne (1951) described a consecutive pathological series of the lungs of mineral-dust workers (1929-1949), and of persons without pneumoconiosis. The prevalence of primary neoplasms of the lung was 8.3% among the 169 controls, 6.9% among 796 silicotics (including coal workers) and 6.7% among 240 people with other forms of pneumoconiosis. [The Working Group noted that no data on smoking habits were available.]

Schüler and Rüttner (1986) examined the mortality of all 2399 cases of silicosis diagnosed in Switzerland 1960-1978. The overall mortality odds ratio for lung cancer for all silicotics was 2.41 ($p < 0.05$). The ratios by industry were as follows: mining and tunnelling workers, 2.51 ($p < 0.001$); stoneworkers, 1.16 (nonsignificant); foundrymen, 3.92 ($p < 0.001$); and ceramic workers, 1.85 (nonsignificant). [The Working Group noted that no data were available on smoking habits or on possible levels of exposure to silica.]

Neuberger *et al.* (1986) calculated the SMR for cancer of the trachea, bronchus and lung among all 2212 Austrian silicotics who died from 1955 to 1979. The overall SMR, adjusted for age and sex, was 148 ($p < 0.001$) in dust-exposed workers. The relative risk for lung cancer in silicotics increased from 1.31 in the 1955-1959 period to 1.42 in 1975-1979. [The Working Group noted that no information was available on smoking habits, occupational exposures or possible levels of exposure to silica.]

(ii) *Epidemiological studies*

Hessel and Sluis-Cremer (1986) studied 127 lung cancer cases and 127 controls in a population of white South African gold miners. Both groups were drawn from the files of the gold miners' pension fund using death certificates from January 1979 to October 1983 and were matched on year of birth, a minimum of at least four years' employment and tobacco consumption ten years prior to death. Cumulative dust exposure was similar in cases and controls. A number of potential controls became cases when autopsy or biopsy results revealed lung cancers. Miners with a history of asbestos exposure were excluded. Silicosis was diagnosed radiographically in 19% of cases and 17% of controls, and at autopsy in 88% of cases and 87% of controls. Analysis revealed no independent association between prior silicosis and lung cancer. [The Working Group noted that the power of the study to detect a difference varied with whether silicosis was diagnosed at autopsy or radiographically. The finding of new lung cancer cases among an unspecified number of candidate controls suggests that there could have been bias due to misclassification.]

Steenland and Beaumont (1986), in their study of mortality in the US granite workers' union, found that silicosis was mentioned on the benefits records of 26/97 lung cancer cases and on those of 14/135 persons who died of other cancers. The resulting odds ratio of 3.16 was significant at $p = 0.001$. [The Working Group noted that no data on smoking habits were available.]

Forastiere *et al.* (1986) conducted a case-referent analysis of lung cancer deaths in Civitacastellana, Italy, during the period 1968-1984 in relation to occupational exposure and smoking habits. Seventy-two cases and 319 referents who died from other causes and

matched by age and year of death were included in the analysis; 20.8% of cases and 7.8% of controls were silicotics. The odds ratios were 1.0 (95% confidence interval, 0.4-2.4) for exposure in quarries, 1.4 (0.7-2.8) for nonsilicotics exposed in the ceramics industry and 3.9 (1.8-8.3) for silicotics exposed in the ceramics industry.

Westerholm (1980) conducted a cohort mortality study of workers compensated for silicosis from the Swedish Pneumoconiosis Register from 1931 to 1969. For those whose silicosis arose from employment in mining, quarrying and tunnelling and was diagnosed between 1931 and 1948, the SMR for lung cancer was 590 ($p < 0.01$); for those whose silicosis was diagnosed from 1949 to 1969, the SMR was 380 ($p < 0.01$). Among workers in the iron and steel industry whose silicosis occurred between 1949 and 1969, the SMR for lung cancer was 220 ($p < 0.05$). [The Working Group noted that data on smoking habits were not available.]

Westerholm *et al.* (1986) followed up 712 silicosis cases (248 in mining, quarrying and tunnelling and 428 in the iron and steel industry), drawn from the Swedish silicosis registry (1959-1977), and 810 people without silicosis recorded in the Swedish silica exposure registry and followed up between 1961 and 1980. All persons on the latter registry had had at least five years' occupational exposure to silica. The rate ratios for death from lung cancer were 4.1 ($p < 0.05$) for mining, quarrying and tunnelling workers and 1.8 for iron and steel workers. [The Working Group noted that no data were available on smoking habits or on cumulative dust exposure, and that the case and control groups may not have been comparable.]

Finkelstein *et al.* (1982) studied 1190 miners in Ontario, Canada, who had been compensated for silicosis in 1940 to 1975. An overall SMR of 198 (45 observed, 22.7 expected; $p < 0.01$) was recorded in comparison with provincial rates, with SMRs of 303 ($p < 0.01$) and 195 ($p < 0.05$) for silicotics diagnosed between 1940 and 1949 and between 1950 and 1959, respectively. The data showed a SMR for lung cancer of 248 (38/15.3) for silicotics diagnosed between 1940 and 1959; for silicotics diagnosed between 1960 and 1975, seven cases of lung cancer were observed, with 7.4 expected. [The Working Group noted that no data on smoking habits were available, and that exposures may have included radon, nickel, chromium and other metals.]

Finkelstein *et al.* (1986) examined the risks for lung and stomach cancer among 276 men who had been employed in industries in Ontario, Canada, excluding underground mining and foundry work but including ceramic and pottery, granite and quarry workers, silica-brick makers and people working in sandblasting and with silica flour and abrasives, who had been compensated for silicosis from 1940 to 1984 and followed up until June 1985. The SMR for lung cancer was 302 (16 observed, 5.3 expected; $p < 0.01$) and that for stomach cancer, 366 (7 observed, 1.9 expected; $p < 0.01$). Elevated risks for lung cancer were reported for ceramic workers (SMR, 293; 6 observed, 2.05 expected), granite and quarry workers (SMR, 357; 5/1.4) and silica-brick makers (SMR, 183; 2/1.1). [The Working Group noted that data on smoking habits were available for only 75% of the population.]

Gudbergsson *et al.* (1984) conducted a study among 331 male cases of silicosis during 1964-1974, from the Finnish Registry of Occupational Diseases. The cohort was followed until the end of 1975, and their cancer incidence was compared with the age-adjusted

incidence from the Finnish Cancer Registry. There was a standardized incidence ratio of 3.0 (18 observed, 6.0 expected) for lung cancer, with a 99% confidence interval of 1.5-5.3. The incidence for all other cancers was equal to that of the general Finnish male population. The average exposure to silica dust among the lung cancer subgroup was 23 years and did not differ from that in the whole silicotics group. [The Working Group noted that no data were available on smoking habits, on specific occupations or on latency.]

Kurppa *et al.* (1986) examined the mortality of 961 cases of silicosis diagnosed in Finland from 1935 to 1977. Using the Finnish male population as a comparison, they observed a SMR of 312 for cancer of the lung, trachea and bronchus (80 observed, 25.6 expected; 99% confidence interval, 230-414). A SMR of 161 (6/3.7) was found for cancers of the haematopoietic system, and SMRs of 704 for pulmonary disease (165/23.4) and of 738 for tuberculosis (130/17.6). When examining the lung cancer risk by industry, the SMRs for cancer of the lung, trachea and bronchus were as follows: mining, 436 (99% confidence interval, 264-670); stone industry, 271 (112-549); steel casting, 184 (54-451); iron foundries, 225 (88-465); and other industries, 343 (168-628). The authors demonstrated that SMRs for each industry were increased by 40% or more (despite small numbers), regardless of whether the silicosis had been diagnosed between 1935 and 1959 or between 1960 and 1977. [The Working Group noted that no data were available on smoking habits or on the frequency of autopsy.] When the results were analysed according to the Johannesburg radiographic classification (Gardner *et al.*, 1930), the SMRs were 416 for silicotuberculosis, 377 for incipient findings and 294 for definite findings.

Zambon *et al.* (1986) examined the mortality of a cohort of 1234 people from the Veneto region of Italy who had been compensated for silicosis in 1959-1963 and followed through 1980. Complete occupational and smoking histories were obtained by interview of the subjects at the time of compensation. Overall, the SMR for tuberculosis was 1960 and that for respiratory disease (silicosis), 741. There was a significant ($p < 0.05$) SMR for lung cancer of 228 and a nonsignificant SMR of 206 for larynx (based on only seven cases). The number of deaths from lung cancer increased with the number of years since first silica exposure. Workers were derived from a variety of industries, including mining, tunnelling and quarrying; tunnelling and quarrying industries had significant overall SMRs of 239 and 569, respectively. Zambon *et al.* (1985) followed up 1332 of the same persons until 1984, and found SMRs of 1961 for tuberculosis, 785 for silicosis, 249 for lung cancer and 195 for laryngeal cancer, based on eight cases. In nonsmokers (based on small numbers), the SMR for lung cancer increased from 0 in workers exposed to silica for nine years or less (0 observed, 1.6 expected) to 77 (1/1.3) for those exposed for 10-19 years and to 476 (3/0.6) for those exposed for 20 years or more. In smokers (based on larger numbers), the corresponding SMRs were 279 (19/6.8), 292 (21/7.2) and 375 (12/3.2). [The Working Group noted that, since the expected values for cancer risk were derived from the general population, they underestimate for smokers and overestimate for nonsmokers.]

Chirotani (1984) noted a rise in the relative risk of lung cancer in one Japanese hospital treating silicotics. The author examined the lung cancer risk among hospitalized cases of pneumoconiosis between 1971-1975 and 1976-1981, using the rates for the Japanese general male population over 50 years of age as expected values, and reported a SMR for all

pneumoconioses of 575 (48 observed, 8.35 expected) during the years 1979–1981. For silicosis, the SMR was 653 (34 observed, 5.21 expected), while for anthracosilicosis it was 491 (14 observed, 2.85 expected). When the risk was assessed by the International Labour Office (1980) X-ray classification for all pneumoconioses combined, the author indicated that the risk was greatest for smaller opacities, especially category 2. For large opacities, there was a gradient rising from A to C, but the numbers of cases were very small. The author indicated that the SMRs were 600 (26/4.35) and 660 (19/2.88) for current and ex-smokers, respectively; the SMR was 268 (3/1.12) for nonsmokers, indicating confounding or effect modification in the data. [The Working Group noted that the study was based on a comparison of hospitalized cases with the general population, and that the authors did not indicate whether their X-ray readers were unaware of the case/referent status of the person whose film they were looking at.]

Rubino *et al.* (1985) carried out a proportionate mortality analysis of 746 workers compensated for silicosis in Piedmont, Italy, during the period 1970–1983. A statistically significantly raised ratio was observed for lung cancer (1.36; 81 observed, 59.5 expected; $p < 0.05$). The major contribution to the excess was from foundry workers (1.59; 56 observed, 35.2 expected; $p < 0.05$). [The Working Group noted that data on smoking habits were not available.]

[The Working Group noted that in all of these studies of silicotics, there are methodological difficulties, including noncomparability of referent subjects, differences between countries in the definition of compensational silicosis, possible differences in disease detection methods, probable differences in smoking prevalence and confounding occupational exposures. All of these factors may bias silicosis registry-based case-control studies in the direction of a silicosis-lung cancer association. Alternatively, silicosis is associated with increased mortality from cor pulmonale, tuberculosis and infectious diseases, which may serve as competing risks for lung cancer. These factors make silicosis case registry-based case-control studies difficult to interpret.]

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Silica minerals are ubiquitous in the earth's crust in both crystalline and amorphous forms. The presence of silica in the environment results from natural processes and from human activity. Occupational exposures occur in many different industries and under a wide range of circumstances. Millions of workers in mining and quarrying, steel, iron and other metal foundries, construction, glass and ceramics production and the granite and stone industries are among those most frequently exposed to silica-containing dusts. Respirable silica levels vary widely both within given industrial sectors and between different workplaces within the same sector.

High exposures have been measured in industries producing high-purity sands and silica flours of small particle size, during sandblasting and in stone quarrying and processing.

Occupational exposure to silica nearly always includes exposures to mixed mineral dusts as well as to substances such as asbestos, radon and polynuclear aromatic compounds. Consumers may be exposed through use of silica-containing products.

4.2 Experimental data

Various forms and preparations of crystalline silica were tested by different routes of exposure. Different specimens of quartz, with particle sizes in the respirable range, were tested for carcinogenicity in two experiments in rats by inhalation and in three experiments in rats by single or repeated intratracheal instillation. In these five experiments, there were significant increases in the incidences of adenocarcinomas and squamous-cell carcinomas of the lung. No pulmonary tumour was observed in hamsters in four experiments using repeated intratracheal instillation of quartz dusts. Single intrapleural and intraperitoneal injections in rats of suspensions of several types of quartz resulted in thoracic and abdominal malignant lymphomas, primarily of the histiocytic type. Intrapleural injection of cristobalite and tridymite with particles in the respirable range resulted in malignant lymphomas, primarily of the histiocytic type. No tumorigenic response was observed with one sample of quartz in the strain A mouse lung adenoma assay. In the studies by inhalation and intratracheal administration, fibrosis was an important part of the biological response to crystalline silica.

Amorphous silica was tested by oral administration to rats, inhalation exposure in mice, intratracheal administration to hamsters, subcutaneous and intraperitoneal injection to mice and intrapleural administration to rats, using different preparations, mostly with poorly-defined physicochemical characteristics. Most of the tests gave negative results or were inadequate. In one test by intraperitoneal injection of uncalcined amorphous silica (diatomite) in mice, an increased incidence of lymphosarcomas in the abdominal cavity was reported. In one inhalation study in mice, a slight increase in the incidence of lung tumours was observed.

The available data were inadequate to evaluate the reproductive or prenatal toxicity of silica to experimental animals.

Silica was not mutagenic to *Salmonella typhimurium* or *Escherichia coli*. Quartz induced micronuclei but not sister chromatid exchanges in mammalian cells *in vitro*. Two samples of quartz induced transformation in Syrian hamster embryo cells in culture. Quartz did not induce micronuclei in mice *in vivo*.

4.3 Human data

No adequate epidemiological data were available to evaluate the carcinogenicity of amorphous silica.

Ore mining and quarrying

Repeated cohort studies of employees of one gold mine, with widely varying duration and intensity of silica exposure, showed substantial exposure-related mortality from

Overall assessment of data from short-term tests: Silica^a

	Genetic activity			Cell transformation
	DNA damage	Mutation	Chromosomal effects	
Prokaryotes	— ^b			
Fungi/Green plants				
Insects				
Mammalian cells (<i>in vitro</i>)		?		+
Mammals (<i>in vivo</i>)		—		
Humans (<i>in vivo</i>)				
Degree of evidence in short-term tests for genetic activity: Inadequate				Cell transformation: Positive

^aThe groups into which the table is divided and the symbols ‘+’, ‘—’ and ‘?’ are defined on pp. 19-20 of the Preamble; the degrees of evidence are defined on pp. 20-21.

^bPhysical form of sample not specified

silicosis, tuberculosis and heart disease; no consistent increase in mortality from respiratory or other cancers was observed. Other cohorts of metal miners have had high mortality from silicosis and mortality rates for respiratory cancer some 20-50% above expected levels. The contributions of cigarette smoking and other occupational exposures, radon in particular, were not assessed.

Coal mining

Numerous studies have been conducted of cancer mortality in coal miners. The only study that examined quantitative relationships between exposure to silica and lung and digestive cancers showed no significant association. Studies of workers with coal-miners' pneumoconiosis also generally showed no association with lung cancer.

Granite and stone industry

Five epidemiological studies of workers in the stone and granite industry reported excess mortality from nonmalignant respiratory disease (especially silicosis). One study of tunnel workers reported significant excess mortality from respiratory cancer, the risk rising with duration of employment; exposure to radon was likely but was not mentioned. Three studies of granite workers reported small excesses of lung cancer mortality but lacked information on smoking. One further study of a population of granite workers reported excess mortality from gastrointestinal cancer.

SILICA

111

Ceramics, glass and related industries

The relationship between employment in ceramics, glass and related industries and lung cancer was examined in one proportionate mortality study, one case-control study and one cohort study. All showed an approximately two-fold increase in the risk for lung cancer. Only the case-control study took smoking into account.

Foundries and metallurgical industries

Studies in foundry workers, who are potentially exposed to a wide variety of carcinogenic materials, have consistently shown moderate increases in the incidence of silicosis and in mortality from lung cancer. In several of these studies, mortality from nonmalignant respiratory disease and lung cancer increased with duration of employment.

Silicotics

A number of studies have investigated the occurrence of lung cancer in persons diagnosed as having silicosis after occupational exposure to dust containing crystalline silica. Of three case-control studies, two showed an association between silicosis and lung cancer. Seven cohort studies and one proportionate mortality study all demonstrated that lung cancer occurs more frequently in silicotics than in the general population. This increase has been seen among miners, quarry workers, foundry workers, ceramic workers, granite workers and stone cutters. In some of these studies, the risk of lung cancer increased with duration of employment. Only rarely, however, were data on smoking and on potential confounding exposures obtained and the comparability of the referent population assured.

4.4 Evaluation¹

There is *sufficient evidence* for the carcinogenicity of crystalline silica to experimental animals.

There is *inadequate evidence* for the carcinogenicity of amorphous silica to experimental animals.

There is *limited evidence* for the carcinogenicity of crystalline silica to humans.

There is *inadequate evidence* for the carcinogenicity of amorphous silica to humans.

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¹For definition of the italicized terms, see Preamble, pp. 18 and 22.

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SILICA

137

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WOLLASTONITE

1. Chemical and Physical Data

1.1 Synonyms and trade names

CAS Registry No.: 13983-17-0

Chem. Abstr. Name: Wollastonite

Synonyms: Aedelforsite; gillebächite; okenite; rivaite; schalstein; tabular spar; vilnite (Andrews, 1970)

Trade names: Cab-O-Lite; Casiflux; F1; FW50; FW200; FW325; NCI-C55470; Nyad; Nyad G; Nycor; Tremin; Vansil; Wollastokup

1.2 Structure of typical mineral

Molecular formula: CaSiO_3

Natural wollastonite occurs as triclinic and monoclinic varieties, which are very difficult to distinguish. When triclinic, its unit cell parameters are: $a = 0.79$, $b = 0.73$ and $c = 0.71$ nm; $\alpha = 90^\circ 02'$, $\beta = 95^\circ 22'$ and $\gamma = 103^\circ 26'$ (Deer *et al.*, 1978).

Originally, it was classified as a pyroxene group mineral, but it has since been shown to have a slightly different chain structure. It consists of infinite chains containing three SiO_4 tetrahedra per unit cell, with the tetrahedra joined apex to apex; one of the tetrahedra is orientated with an edge parallel to the axis of the chain. These chains of tetrahedra are paired and offset slightly to produce the differences in structural forms of the mineral. Calcium atoms occur in octahedral coordination and alternate with layers composed of silica atoms between sheets of oxygen atoms (Deer *et al.*, 1978).

1.3 Chemical and physical properties

From Roberts *et al.* (1974), unless otherwise specified

- (a) *Hardness:* 4.5-5 on Mohs' scale
- (b) *Density:* 2.87-3.09
- (c) *Cleavage:* (100) perfect
 - (001) good
 - (102) good

- (d) *Colour:* Brilliant white; may be greyish, pale green or brownish with impurities (Deer *et al.*, 1978; Harben & Bates, 1984)
- (e) *Description:* Crystals commonly tabular; usually massive, cleavable to fibrous; also granular and compact. Twinning on (100) common. Structure changes to monoclinic at 1150°C (1120°C, Elevatorski & Roe, 1983); this form is sometimes called *para*-wollastonite or wollastonite-2M (Andrews, 1970; Deer *et al.*, 1978). A 10% water slurry has a naturally high pH (9.9) (Elevatorski & Roe, 1983).

Wollastonite occurs in coarse-bladed masses, rarely showing good crystal form. Fragments of crushed wollastonite tend to be acicular, lath-shaped or fibrous. The particle length:diameter ratios are commonly 7:1 to 8:1 (Andrews, 1970; Elevatorski & Roe, 1983).

1.4 Technical products and impurities

Wollastonite has a theoretical composition of 48.3% CaO and 51.7% SiO₂, although iron, magnesium or manganese may partially substitute for calcium (Harben & Bates, 1984). The chemical compositions of commercial wollastonite products from several countries are summarized in Table 1.

Table 1. Chemical composition (%) of commercial wollastonite products

Component	Lappeenranta ^a (Finland)	Willsboro, NY ^a (USA)	Belkapahar ^b (India)	Kolkidongai ^c (Kenya)	Santa Fe ^c (Mexico)
SiO ₂	52	51	49	55	52
CaO	45	47	48	42	47
Al ₂ O ₃	0.4	0.3	0.7	0.1	0.5
Fe ₂ O ₃	0.2	0.6	0.4	0.07	0.2
TiO ₂	max 0.05	0.05	traces	0.01	0.06
MnO	max 0.01	0.1	0.1	0.01	0.4
MgO	0.6	0.1	0.06	0.8	0.08
Na ₂ O	0.1	NA ^d	0.02	0.04	0.2
K ₂ O	0.01	NA	0.1	0.04	0.04

^aFrom Anon. (1975)

^bFrom Wolkem Private Ltd (undated)

^cFrom Anon. (1969a)

^dNot available

Wollastonite rarely occurs in pure form, and ores in the major deposits contain 18-97% wollastonite. Associated minerals are most often calcite, quartz, garnet and diopside. The approximate mineral compositions of the major commercial wollastonite deposits are presented in Table 2. Indian ores also contain minor amounts of these minerals (Power, 1986).

WOLLASTONITE

Table 2. Mineral composition (%) of major commercial wollastonite deposits^a

	USA ^a	Finland ^{a,b}	Kenya ^a	New Zealand ^c
Wollastonite	60	90	87	70-90
Garnet	30	—	—	—
Quartz	< 3 ^d	2	13	—
Diopside	10	—	—	—
Calcite	—	3	—	—
Other minerals	—	5	—	—

^aFrom Power (1986)^bData for purified commercial product^cFrom Andrews (1970)^dFrom Zumwalde (1977)

Wollastonite technical materials are marketed in numerous grades. The US manufacturers produce powdered, low-aspect ratio (5:1-10:1) products in several mesh sizes (325-1250) for the ceramics industry, as well as 400 and 1250 mesh high-aspect (15:1-20:1) grades for fillers and asbestos replacement. The Finnish material is available in low-aspect (3:1-4:1) grades with 70-400 mesh-size particles. The most common materials worldwide are 100-300 mesh grades marketed for the ceramics and plastics industries (Power, 1986).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(a) Production

Wollastonite was probably first mined in California in 1933 for mineral wool production. Significant commercial production did not start, however, until about 1950, at the Willsboro, NY, deposit. Since that time, wollastonite has become widely used, especially in the ceramics industries of the USA and Europe (Power, 1986).

The largest commercially exploited deposits are in the USA and Finland, and two mines in those countries provide the basis for the wollastonite industry (Power, 1986). World reserves of rock containing extractable wollastonite have been estimated at 165 million tonnes (Andrews, 1970), although Indian reserves alone have been estimated at over 180 million tonnes (Anon., 1970). The following countries have commercially exploitable wollastonite reserves: Australia, Canada, Chile, China, Finland, Greece, India, Japan, Kenya, Mexico, Namibia, New Zealand, Norway, Poland, Romania, South Africa, Spain, Sudan, Turkey, USA, USSR and Yugoslavia (Anon., 1969b; Andrews, 1970; Roberts *et al.*,

1974; Anon., 1975; Elevatorski & Roe, 1983; Power, 1986). Small quantities of wollastonite have been mined in many of these, although not on a large scale or on a continuous basis (Andrews, 1970).

The original mine in California was worked by open quarrying. An early ornamental use of wollastonite slabs or rocks required simple collection of the materials close to or on the surface, and this probably accounted for much of the early Californian and nearly all of the Mexican production. The first Willsboro, NY, mine (1943) was also worked on the surface (Anon., 1969a). Since 1960, however, at least one of the three New York deposits has been mined principally underground due to the presence of a structurally complex wollastonite vein (Anon., 1975). Mining of the Finnish deposits is largely open cast. Mines in other principal production areas, in India and Mexico, are worked by open pit and open pit-underground combination mining (Andrews, 1970; Anon., 1975).

Refinement of the ore into high-grade wollastonite, which was originally done by manual selection at many mines, is now performed by screening and magnetic separators, sometimes in combination with flotation and vacuum filtration (Andrews, 1970). Grinding and milling operations result in variable mesh powders or aggregates (Power, 1986).

At present, only nine companies worldwide are known to mine and market this mineral. Mining is centred in the USA, where three companies operate; one company in each of the following countries is also known to mine wollastonite: Finland, India, Japan, Kenya, Mexico and New Zealand (Coope, 1982). Production is also thought to occur in China and the USSR (Elevatorski & Roe, 1983; Power, 1986).

The USA is by far the most important producer of wollastonite in the world; most of the production comes from New York State, and a little from California. Production figures in several countries for 1960-1983 are presented in Table 3. Indian production in 1985 has been estimated at 35 000 tonnes. Current annual production levels of two smaller producers, Namibia and New Zealand, are 4800 and 500 tonnes, respectively (Power, 1986); small quantities have also been mined recently in Japan and Turkey (British Geological Survey, 1985). The Sudan, a former producer of small quantities, mined 20 tonnes in 1960 (Andrews, 1970).

Finland exports large quantities to other European countries. The USA uses most wollastonite domestically but exports some to European markets (Andrews, 1970). Similarly, Indian and Mexican products are largely exported. India has relied on German and Dutch markets but at present exports to Japan, Australia and the USA; Mexico has exported most of its wollastonite to Nicaragua and the Federal Republic of Germany (Power, 1986).

(b) Use

Wollastonite was first mined for the production of mineral wool. Although this use exists today, it is minor compared to the uses that have developed since 1950, when major commercial production began. The predominant uses can be grouped into the following broad categories: ceramics, paints, plastics and rubber, abrasives and metallurgical applications (Andrews, 1970; Power, 1986).

WOLLASTONITE

149

Table 3. Wollastonite production by country, 1960-1983 (tonnes)^a

Country	Year					
	1960	1970	1980	1981	1982	1983
Finland	2 342	6 051	8 782	13 690	14 962	15 402
Kenya	—	100	200 (1979)	—	—	—
Mexico	4 500	6 562	20 905	14 602	15 599	10 784
USA	27 000- 36 000	30 000	76 000	87 000	86 000	83 000
India	—	576	5 790	15 915	20 724	16 557

^aFrom Institute of Geological Sciences (1967); Power (1970); Institute of Geological Sciences (1978); British Geological Survey (1985); Power (1986)

Ceramics

Wollastonite is used in some ceramic products, and this use accounts for over half of its consumption worldwide. Wollastonite has several advantages over more typical ceramic raw materials, the most notable being faster firing time. Ceramic materials have included up to 70% w/w wollastonite, and published recipes for ceramic tiles have included 5, 8, 36, 55 and 67% wollastonite, in combination with clays, flint and talc. Other ceramics applications include glazes and fluxes, ceramic artware and dinnerware, and electrical insulating materials (Andrews, 1970).

Paints and coatings

Wollastonite is used as an extender in both oil- and water-based emulsion paints for exterior use, and in latex and road-marking paints. Because of the brilliant nature of its white colour (when very pure), its low oil absorption, high pH and good wetting abilities, it is added to many types of coatings, where it imparts colour, fluidity and mildew resistance. Paint-grade wollastonite, a fine high-purity grade, has been added at levels of 9-13% w/w to many US paints (Andrews, 1970; Anon., 1975).

Plastics and rubber

Wollastonite has been incorporated as a filler in plastics (Power, 1986) because of its colour and structural properties and has been used in epoxy resins as a 50% loading pigment (Andrews, 1970).

Other uses

A current and increasing use of wollastonite is as a replacement for asbestos. Coarser grades of wollastonite are used at up to 50% with other fillers, binders and organic fibres for heat-containment panels. It has also been used for ceiling and floor tiling, brake linings and high-temperature appliances (Power, 1986).

An important European application of natural and synthetic wollastonite is in welding powders and fluxes for metal casting. The structural properties of wollastonite render fluxes useful for insulating molten materials before cooling (Power, 1986).

Wollastonite has also been used in abrasives, in welding electrodes, as a soil conditioner and plant fertilizer, as a substitute for limestone and sand in glass manufacture, as a filler in paper and as a road material (Andrews, 1970; Anon., 1975; Elevatorski & Roe, 1983).

2.2 Occurrence

(a) *Natural occurrence*

Wollastonite occurs most commonly in nature where limestone has reacted at high temperature with igneous rock, resulting in the genesis of two principal mineral types. Wollastonite from 'skarn' deposits (contact metamorphic genesis) is typically of high purity and accounts for most of the world's mined ores. This type is fine-grained and usually interspersed with other silicates. The other type, the carbonatitic wollastonite, is found to a much more limited extent in nature. Wollastonite occurs interspersed among other minerals or as layers of varying purity between rock and mineral deposits (Andrews, 1970; Kuzvart, 1984).

(b) *Occupational exposure*

Airborne dust and fibre concentrations have been measured in the two largest wollastonite production plants in the world (Table 4).

The Finnish quarry produced wollastonite as a side-product of limestone mining. Consequently, the operational stages, from drilling in the open cast mine to fine crushing before froth flotation processing at a separate location, involved mixed exposures to wollastonite fibres and granular calcite dust. On average, the quarried stone contained about 15% wollastonite and 2-3% quartz. A similar mean composition was also found for the respirable fraction of dust samples from mining and milling operations. In drilling, crushing and sorting, the concentration of total dust ranged from 2 to 99 mg/m³ and the levels of airborne fibres from 1 to 45 fibres/cm³, as measured by phase-contrast optical microscopy. In the flotation and bagging plant, dust was mainly composed of wollastonite, and workplace concentrations ranged from 15 to 30 mg/m³ for total dust and from 8 to 37 fibres/cm³ for fibres, as counted by phase-contrast optical microscopy. Combined mean values for samples from breathing zones and stationary samples (as summarized by the Working Group) are shown in Table 4. In all operations, the mean level of respirable quartz was below 0.1 mg/m³. The counting criteria were the same as those most commonly used for asbestos: all fibres over 5 µm in length, less than 3 µm in diameter and with an aspect ratio over 3:1 were counted. When studied by scanning electron microscopy, the thinnest wollastonite fibres were characteristically 0.2-0.3 µm in diameter. The median fibre lengths and median diameter were 4 µm and 0.8 µm in crushing operations and 2 µm and 0.4 µm in bagging work (Huuskonen *et al.*, 1982; Korhonen & Tossavainen, 1982; Huuskonen *et al.*, 1983a).

WOLLASTONITE

151

Table 4. Mean concentrations of total dust and fibres in wollastonite mining and milling

	Total dust (mg/m ³) ^a	Fibres >5 µm in length (fibres/cm ³)	
		PCOM ^{b,c}	SEM ^d or TEM ^e
<i>Lappeenranta, Finland, 1981^f</i>			
Drilling	27		4
Loading and transporting	0.3		
Primary crushing	33	5.1	23
Manual and automatic sorting	15		8
Secondary and fine crushing	34	22	32
Flotation and fine milling	22	21	30
Bagging	27	19	36
No. of samples	69	18	44
<i>Willsboro, USA, 1976-1982^g</i>			
Mining except crushing	0.9	0.3	0.3
Milling and crushing	4.1	19	9.5
Labourer and beneficiator	8.7	20	11
Mill maintenance and packers	10	32	13
No. of samples	97	15	15

^aFull shift sampling^bPhase-contrast optical microscopy^cShort-term sampling^dScanning electron microscopy^eTransmission electron microscopy^fFrom Huuskonen *et al.* (1983a)^gFrom Hanke & Sepulveda (1983); Hanke *et al.* (1984); Zumwalde (1977)

Similar results have been reported from the US wollastonite production plant in Willsboro, NY (see Table 4). In open-cast and underground mining, crushing, packing and maintenance, the mean concentration of total dust ranged from 0.9 to 10 mg/m³. Bulk samples contained less than 2% free silica, and respirable silica concentrations ranged from <0.01-0.13 mg/m³. In the same operations, airborne fibre counts by phase-contrast optical microscopy showed a mean of 0.3 fibre/cm³ in the mine and a range of 0.8-48 fibres/cm³ in the mill. Fibrous particles had a median diameter of 0.22 µm and a median length of 2.5 µm (Zumwalde, 1977; Hanke & Sepulveda, 1983; Hanke *et al.*, 1984).

Where wollastonite has been used in the production of fibre-reinforced cement sheets, airborne fibre levels ranging from 0.02 to 0.2 fibre/cm³ have been measured during stacking and mixing (Danish National Institute of Occupational Health, 1986).

(c) Nonoccupational exposure

Consumer products generally contain wollastonite that has been subjected to physico-

chemical processes that irrevocably alter its original identity and form. Such products include tiles, cements for abrasive wheels and porcelains (Kuzvar, 1984).

2.3 Analysis

In dust samples, wollastonite may be analysed by phase-contrast optical microscopy, X-ray diffractometry and electron microscopy. Identification of wollastonite fibres may be achieved by means of microanalysis and selected area electron diffraction; the silicon:calcium ratios and structural data are obtained for individual particles (Zumwalde, 1977; Tuomi *et al.*, 1982; Huuskonen *et al.*, 1983a). When characterized on the basis of diagnostic X-ray reflections in powder diffraction pattern, the strongest lines appear at 0.297, 0.352 and 0.383 nm (Roberts *et al.*, 1974). Triclinic and monoclinic wollastonite can be distinguished as lines of 0.405 and 0.437 nm, respectively, adjacent to a common 0.383 line (Deer *et al.*, 1978).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals¹

Intrapleural administration

Rat: Groups of 30-50 female Osborne-Mendel rats, 12-20 weeks of age, received a single application of wollastonite [purity unspecified] particles by intrapleural implantation, through thoracotomy, of a coarse fibrous pledge on one side of which was spread 1.5 ml of 10% gelatin (Stanton & Wrench, 1972) containing 40 mg wollastonite. Four separate grades of wollastonite from the same Canadian mine were used. The rats were followed for two years and survivors were then killed. The incidences of pleural sarcomas were: grade 1, 5/20; grade 2, 2/25; grade 3, 3/21; grade 4, 0/24; compared with 14/29 animals treated with UICC crocidolite asbestos, 3/491 untreated controls in the same study and 17/615 in a control group receiving pleural implants of 'nonfibrous materials' described by the authors as 'noncarcinogenic'. [The incidence of pleural sarcomas was statistically significantly higher ($p < 0.05$, Fisher exact test) in groups receiving grades 1 and 3 than in the controls receiving pleural implants.] (Stanton *et al.*, 1981). [The Working Group noted that none of the grades of wollastonite contained fibres $> 8 \mu\text{m}$ in length and $< 0.25 \mu\text{m}$ in diameter (the hypothetical range for maximal carcinogenesis: Stanton *et al.*, 1981). All the grades contained fibres 4-8 μm in length and $< 0.5 \mu\text{m}$ in diameter, but grade 4 contained very few fibres with these dimensions.]

¹The Working Group was aware of two studies in progress in rats, one by inhalation and one by intraperitoneal injection (IARC, 1986).

WOLLASTONITE

153

3.2 Other relevant biological data

(a) Experimental systems

Toxic effects

No data were available on the toxic effects of mineral wollastonite *in vivo*.

The effects of wollastonite *in vitro* have been studied by several laboratories, with discordant results. A dose of 0.5 mg/ml of a naturally occurring fibrous wollastonite from the USA and of a natural, almost nonfibrous specimen from Finland were haemolytic to human red blood cells. However, these samples caused less haemolysis than nonfibrous synthetic wollastonite or UICC chrysotile asbestos (Skaug & Gylseth, 1983). The toxicity of wollastonite to LLC-MK₂ (monkey kidney) cells was found to be comparable to that of asbestos minerals. Following exposure to 5 mg/ml, cell survival was approximately 50%, as measured by trypan blue dye exclusion. However, in contrast to asbestos, wollastonite enhanced the induction of interferon in influenza virus-infected LLC-MK₂ cells, but not in uninfected cells. The extent of enhancement was dependent on fibre size, being maximal after treatment with fibres of a mean length of 8.3 µm. Reagent-grade calcium metasilicate (synthetic wollastonite) did not enhance interferon production, suggesting that either the structure of, or the presence of a nonsoluble contaminant on, wollastonite was responsible for the induction (Hahon *et al.*, 1980).

Pasanen *et al.* (1983) investigated the effects of Finnish wollastonite (fibre diameter, approximately 0.5 µm; length, 2–5 µm) on rat alveolar macrophages. The parameters assessed were cell viability (trypan blue exclusion), release of cytoplasmic lactate dehydrogenase (LDH), release of lysosomal β-glucuronidase and fibre uptake. After exposure to 25 µg/ml wollastonite, cell viability was reduced by 15% and LDH release increased by 125% within 24 h; no significant effect on β-glucuronidase release was observed. In exposed cultures, wollastonite was more toxic than titanium dioxide but less toxic than UICC crocidolite; its effect on LDH release was similar to that of titanium dioxide but smaller than that of crocidolite. Macrophages took up less wollastonite than crocidolite 1 h after exposure.

Skaug *et al.* (1984) also used LDH and β-glucuronidase release by mouse peritoneal macrophages to assess the cytotoxicity of samples of US wollastonite (50% of fibres >10 µm) and Finnish wollastonite (3% of fibres >7 µm in length). In contrast to the observations of Pasanen *et al.* (1983), Skaug *et al.* observed induction of a dose-dependent release of β-glucuronidase by Finnish wollastonite and a lower induction by US wollastonite 18 h after exposure. In addition, concentrations of up to 40 µg/ml US wollastonite did not induce release of LDH, whereas the Finnish sample induced significant release of this enzyme. Results from studies on the effect of wollastonite on rabbit alveolar macrophages (Pailes *et al.*, 1984) differed from those on mouse and rat cells (Pasanen *et al.*, 1983; Skaug *et al.*, 1984), leading to the conclusion that a sample of US wollastonite (fibre length, 98% ≤ 8 µm) had little effect on the biochemical or physiological parameters of rabbit macrophages. In comparison to chrysotile asbestos fibres (74% ≤ 8 µm), exposure to up to 250 µg/ml wollastonite for 70 h did not affect cell viability (trypan blue exclusion) or

the release of LDH or β -glucuronidase. Further, wollastonite did not affect oxygen consumption or β -galactosidase activity in rabbit macrophages, but was comparable to chrysotile in inducing the release of acid phosphatase activity.

The effects of wollastonite (US; most fibres, 4-9 μm in length) on rat pulmonary macrophages were assessed using as parameters percentage of ruffled macrophages and ability to phagocytose carbonyl iron beads. Wollastonite was found to decrease both parameters significantly, but to a lesser extent than crocidolite. In addition, wollastonite activated rat serum complement, as measured in a chemotaxis bioassay (Warheit *et al.*, 1984).

Effects on reproduction and prenatal toxicity

No data were available to the Working Group.

Deposition, clearance and retention

No data were available to the Working Group.

Mutagenicity and other short-term tests

No data were available to the Working Group.

(b) *Humans*

Toxic effects

Results from studies in 1981 on 46 men exposed to wollastonite for an average of 21.5 years (10-41 years) in a Finnish quarry have been reported (Huuskonen *et al.*, 1983a). [Exposure conditions are described in section 2.2(b).] Chronic bronchitis was found in 11/46 workers (including 3/15 nonsmokers). Chest radiographs showed small irregular parenchymal opacities (grade 1/0 or 1/1) in seven, pleural thickening only (grade ≥ 3) in six men and both lung and pleural changes in seven; among the 138 referents, five had pulmonary fibrosis only, six had pleural thickening only, and one had both lung and pleural changes. Differences in smoking habits did not account for these changes (Huuskonen *et al.*, 1983b).

In Willsboro, NY, USA, surveys were conducted at a wollastonite mine and mill in 1976 (Shasby *et al.*, 1979) and in 1982 (Hanke *et al.*, 1984). [Exposure conditions are described in section 2.2(b).] Pneumoconiosis (small rounded opacities; category 1, type q profusion) was observed in 4/76 wollastonite workers in 1976 and in 3/108 in 1982, and lung function tests suggested mild dust-related limitation of air flow, as reflected by declines in the ratio of forced expiratory volume in one second (FEV_1): forced vital capacity (FVC) and peak flow rate. No pleural change was noted.

Effects on reproduction and prenatal toxicity

No data were available to the Working Group.

Deposition, clearance and retention

No data were available to the Working Group.

WOLLASTONITE

155

Mutagenicity and chromosomal effects

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity to humans

Huuskonen *et al.* (1983b) conducted a cohort study of mortality among 192 male and 46 female workers who had been on the payroll of a Finnish limestone-wollastonite quarry for at least one year. The study covered the period 1923-1980, and the cohort was followed from first employment in the quarry. Causes of death were obtained from death certificates, and numbers of observed deaths were compared with those expected from national age- and sex-specific death rates for 1952-1972. By the end of 1980, 79 deaths had occurred in the cohort *versus* 96 expected. Death was due to malignant neoplasms (all sites combined) for ten men (15.6 expected) and two women (three expected). When the analysis was restricted to workers with ten years since first exposure, the mortality rate for cancer at all sites was not increased: eight observed, 13.2 expected in men; two observed, 2.6 expected in women. Mortality from cancer of the lung and bronchus was: four observed, five expected in men and none observed, 0.2 expected in women. A rare malignant mesenchymal tumour of the retroperitoneum occurred 30 years after first exposure in a 73-year-old nonsmoking woman who had held various production jobs in the quarry for 16 years; her occupational history did not reveal any other dust exposure. The authors noted that past exposures for the cohort could not be determined in detail and that reliable information on smoking habits was unobtainable. [The Working Group noted that follow-up did not account for a one-year minimum from first employment; accordingly, the expected number of deaths was slightly underestimated. The statistical power of this small study to detect a doubling in mortality from lung cancer was only 54% by a one-sided test for significance.]

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Wollastonite occurs in various geological formations around the world. Occupational exposure to wollastonite dusts occurs during mining, milling and production. Consumers may be exposed to altered wollastonite, as in ceramics, although exposure to unaltered mineral may occur through use of products such as paints.

4.2 Experimental data

Four grades of wollastonite of different particle sizes were tested for carcinogenicity in one experiment in rats by intrapleural implantation. A significant increase in the incidence of pleural sarcomas was observed with two grades, and a nonstatistically significant increase with a third grade, all of which contained fibres $>4 \mu\text{m}$ in length and $<0.5 \mu\text{m}$ in diameter. Pleural sarcomas were not observed after implantation of the grade that contained relatively few fibres with these dimensions.

No data were available to evaluate the reproductive or prenatal toxicity of wollastonite to experimental animals or its activity in short-term tests for genetic and related effects.

4.3 Human data

Mild parenchymal and pleural changes have been observed in the lungs of wollastonite workers.

In a small cohort mortality study of workers in a wollastonite quarry, the observed number of deaths from cancer was not higher than that expected.

4.4 Evaluation¹

There is *limited evidence* for the carcinogenicity of wollastonite to experimental animals.

There is *inadequate evidence* for the carcinogenicity of wollastonite to humans.

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¹For definitions of the italicized terms, see Preamble, pp. 18 and 22.

WOLLASTONITE

157

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ATTAPULGITE¹

1. Chemical and Physical Data

1.1 Synonyms and trade names

CAS Registry No.: 12174-11-7

Chem. Abstr. Name: Palygorskite

Synonyms: Palygorskite

Trade names: Attaclay; Attacote; Attagel; Attasorb; Diluex; Min-U-Gel FG; Permagel; Pharmasorb-colloidal; 2000/P-RVM; RVM-FG; X-250; Zeogel

1.2 Structure of typical mineral

Molecular formula: $(\text{Mg}, \text{Al})_2 \text{Si}_4\text{O}_{10}(\text{OH}) \cdot 4\text{H}_2\text{O}$

The structure of attapulgite is similar to that of minerals of the amphibole group and differs only in minor respects from that of sepiolite. In attapulgite, the basic sheet unit is smaller in the 'b' axis direction of the crystal. The units themselves are combined in an identical fashion to those of sepiolite, with the indefinite development of these units along the 'c' axis of the crystal, resulting in an amphibole-like double chain of SiO_4 tetrahedra (Harben & Bates, 1984). The structure formed has been shown to be either orthorhombic or monoclinic. Orthorhombic samples possess cell parameters of $a = 1.27-1.28$, $b = 1.79$ and $c = 0.52-0.53$ nm; monoclinic varieties display unit cell parameters of $a = 1.27-1.28$, $b = 1.78-1.81$, $c = 0.51-0.52$ nm and $\alpha = 92^\circ 14'$ and $\beta = 95^\circ 46'-95^\circ 50'$ (Christ *et al.*, 1969). As with sepiolite, the structural arrangement of attapulgite results in long, thin or lath-like crystals (Anon., 1978).

1.3 Chemical and physical properties (from Roberts *et al.*, 1974)

- (a) *Hardness:* Soft
- (b) *Density:* 2.2
- (c) *Cleavage:* (110) easy

¹Palygorskite is the mineralogical name for attapulgite; however, the commercial term attapulgite is used in literature on its health effects.

- (d) *Colour:* White, grey; translucent; dull
- (e) *Description:* Occurs as elongated, lath-shaped crystals, in bundles that comprise thin sheets composed of minute interlaced fibres

1.4 Technical products and impurities

The chemical compositions of two attapulgite ores (from Spain and the USA), and typical analysis of a widely used attapulgite technical product, are presented in Table 1.

Table 1. Chemical composition (%) of technical attapulgite

Component	Attapulgite ore		Commercial product ^c (as dry weight)
	Attapulgus, GA, USA ^a	Torrejon, Spain ^b	
SiO ₂	54	52	68
Al ₂ O ₃	9	10	12
Fe ₂ O ₃	3	2	5
FeO	0.2	0.5	NA
TiO ₂	0.2	NA	0.7
CaO	2	NA	2
MgO	10	12	11
Na ₂ O	0.03	NA	NA
K ₂ O	0.4	NA	1
P ₂ O ₅	NA ^d	NA	1
H ₂ O	21	22	—

^aFrom Patterson & Murray (1975)

^bFrom Galan & Castillo (1984)

^cFrom Engelhard Corp. (1985)

^dNot available

Attapulgite is found in association with sepiolite, phosphates, carbonates, opal, quartz, cristobalite, montmorillonite and other clay minerals (Galan & Castillo, 1984; Clarke, 1985), and the purity of marketed products is heavily dependent on the mined ore. A major US producer has marketed a beneficiated attapulgite product 80-90% pure (Haas, 1972). The ores in the major Spanish deposit contain 66-90% attapulgite (Galan & Castillo, 1984).

Attapulgite technical products are prepared and marketed to meet specific consumer demands. It is sold in dry sorbent grades and in dry and liquid gellant or colloidal forms. Dry grades are available in many particle sizes; one super-heated material, known as 'low volatile material', resists breakdown in water (Anon., 1978; Engelhard Corp., 1985). The most common use, that of absorbents, relies on the mineral's natural high porosity and sorptivity. Sorptive grades are produced in various mesh sizes and may be calcinated to increase

absorption of larger molecules such as pigments (Haas, 1972; Jones, 1972). Gellant or colloidal grades have more free moisture, higher amounts of volatile matter and are usually finer than sorptive grades. Gellant grades also contain larger amounts of attapulgite than of other clay minerals (Clarke, 1985; Engelhard Corp., 1985).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(a) *Production*

Attapulgite, as a component of various naturally occurring clays, was probably used in ancient times in pottery and for removing oil in cloth manufacture (Jones, 1972).

Attapulgite has been grouped with sepiolite and loughlinite (sodium sepiolite) into a mineral subgroup of hormitic clays. The names of generic clay products may refer to a combination of minerals. For instance, the name 'fullers' earth', a product originally used to absorb fat from wool (fulling), is used in the USA to connote attapulgite, whereas in the UK, it is applied to a certain bentonite (montmorillonite) (Anon., 1978).

Attapulgite was probably first mined in the USA, near Attapulgus, Georgia, the origin of the common industrial name for this mineral. This deposit, consisting of 20-80% attapulgite, is over 60 km in length, extending into northern Florida, and may be one of the largest hormitic clay deposits in the world (Anon., 1978; Clarke, 1985). It is thought to have resulted from seawater sedimentation during the Miocene period (Harben & Bates, 1984; Clarke, 1985). Attapulgite was so named in 1935 by De Lapparent, who examined fullers' earth samples from Attapulgus, GA, Quincy, FL, and Mormoiron, France (Grim, 1968).

Attapulgite is currently mined in eight countries: Australia, France, India, Senegal, South Africa, Spain, Turkey and the USA (Clarke, 1985). Limited production also occurs in the USSR (Ovcharenko & Kukovsky, 1984). The USA is overwhelmingly the largest producer, with four companies mining the Attapulgus area deposits. One company in each of the other listed countries is apparently involved in mining operations (Clarke, 1985).

Attapulgite deposits are mined by open-pit techniques. In US operations, the overburden and clay are stripped by draglines and the ore is transported to nearby plants for milling to coarse (<3 cm) size, after which it is dried and subjected to further refinement (Anon., 1978). Conventional milling and screening techniques are used, in combination with calcination and extrusion, to produce various grades of clay products. One large US firm claims to market a 80-90% pure attapulgite, obtained by dry-beneficiating their 70-80% pure clay ores (Haas, 1972).

In 1983, the production volume of the western world was estimated to be approximately 1.1 million tonnes. US mining companies produced about 84%; the market percentages of other significant producers were Senegal, 9%; Spain, 4%; Australia, 2.5%; and South Africa, 0.5% (Clarke, 1985). US production of attapulgite in 1984 was 852 000 tonnes (Ampian, 1984).

The USA is the world's largest exporter of attapulgite, especially to Canada (US Department of Commerce, 1984; British Geological Survey, 1985). Attapulgite from Senegal is exported mainly to the UK and western Europe (Clarke, 1985; Le Berre, 1985); Australian products are marketed extensively in Taiwan, New Zealand and Japan; and Japan also imports a small amount from Turkey. Spanish mines supply mainly domestic consumers (Clarke, 1985). Production figures for several countries in 1979 to 1983 are presented in Table 2.

Table 2. Attapulgite production by country, 1979-1983 (1000 tonnes)^a

Country	Year					
	1979	1980	1981	1982	1983	1984
Senegal	13	28	33	99	100	-
South Africa	4	4	5	5	4	-
Spain	62	48	47	43	43	-
USA	870	840	831	777	934	852

From Ampian (1980, 1982, 1984); British Geological Survey (1985)

(b) Use

Over 80 specific uses for attapulgite have been reported (Haas, 1972).

Attapulgite was probably first used inadvertently as a component of clay materials such as fullers' earth. Use of fairly pure attapulgite probably began in the USA, where the mineral was first identified (Anon., 1978). It was first sold as a drilling mud in 1941 (Patterson & Murray, 1975); in 1945, it was used primarily for processing mineral and fatty oils (Haas, 1972). During the subsequent 25 years, its use shifted to absorbent applications, such as incorporation in pet litter and materials for cleaning up spills. Uses in the USA are presented in Table 3.

Uses have not been categorized for other countries, but recent market evaluations suggest that the major US uses are fairly representative of world uses (Anon., 1978; Clarke, 1985).

The most common use is now as absorbents, especially for pet wastes. Of the gellant applications, the most important is drilling muds, especially in salt-water oil drilling. Attapulgite is mixed with water, barite and other compounds to form a suspension, or mud, which is used to surround the drill bit and string in the drilling shaft. Attapulgite drilling muds are preferred to other clay muds in ocean drilling because they do not lose swelling capacity in salt water (Patterson & Murray, 1975; Clarke, 1985; US Environmental Protection Agency, 1985).

The colloidal properties of attapulgite have also been exploited in paints, adhesives, sealants and catalysts (Patterson & Murray, 1975; Anon., 1978).

ATTAPULGITE

Table 3. Uses of attapulgite in the USA in 1984^a

Use	Percent
Adhesives	0.2
Animal feed	1.4
Drilling muds	12.5
Fertilizers	6.1
Filtering, clarifying, decolourizing oils and greases	2.1
Cosmetics, pharmaceuticals	0.01
Oil and grease absorbents	24.7
Paints	0.8
Pesticides and related products	11.3
Pet waste absorbents	34.4
Paper filling, roofing	3.1
Miscellaneous	3.4

^aFrom Ampian (1984)

Attapulgite may be used in various other consumer products, including fertilizers, pesticides, cosmetics and pharmaceutical products (Ampian, 1984).

2.2 Occurrence

(a) Natural occurrence

Attapulgite occurs commonly in clay deposits and in calcareous soils, lake-bed sediments and shallow, warm seas in arid and semi-arid climates around the world. These deposits occur in two regions, 20°-40°N latitude and 10°-35°S latitude, as equatorial belts (Callen, 1984).

Attapulgite is mainly sedimentary in origin; it occurs in present-day marine sediments, but areas that are exploited commercially consist of ancient lagoonal or lacustrine deposits. These bedded deposits normally consist of layers of attapulgite mixed in variable amounts with other clay minerals such as illite, sepiolite, montmorillonite and kaolinite. The deposits may also contain appreciable quantities of calcite and phosphate minerals. As with sepiolite, the mineral occurs as massive aggregates of fine individual particles, and bulk specimens display a low specific gravity and high surface area (Callen, 1984; Galan & Castillo, 1984; Ovcharenko & Kukovsky, 1984; Clarke, 1985).

The abundance of attapulgite varies greatly, and it often occurs at trace quantities in clay admixtures. In commercially worked deposits, attapulgite and related fibrous clay minerals attain concentrations of greater than 50% by weight of the clay. Frequently, attapulgite deposits are naturally admixed with variable amounts of carbonate and salt minerals and alternate with beds and lenses of silts, sands and marls (Callen, 1984; Galan & Castillo, 1984).

(b) Occupational exposure

In 1976, about 200 dust samples were collected at various milling operations in a US attapulgite production plant. During crushing, milling, drying and screening, the average concentrations in the workers' breathing zone ranged from 0.05 to 2.1 mg/m³ for total dust and from 0.02 to 0.32 mg/m³ for respirable dust. Except for some individual samples, respirable free silica exposures calculated for each job category were below 0.05 mg/m³. As determined by transmission electron microscopy, airborne attapulgite fibres had a count median diameter of 0.07 µm and a median length of 0.4 µm, with ranges of 0.02 to 0.1 µm in diameter and 0.1 to 2.5 µm in length (Zumwalde, 1976).

Dust concentrations were measured in several hundred air samples in two US companies mining and milling attapulgite clay (Table 4). The mean concentration of total dust ranged from 0.6 to 3.1 mg/m³ in mining and from 0.1 to 23 mg/m³ in milling and shipping operations. On average, the concentration of respirable dust was below 5 mg/m³ in all job categories (Gamble *et al.*, 1986).

Table 4. Mean concentrations (mg/m³) of total and respirable dust^a in two US attapulgite production plants^b

Operation or area	Company A		Company B	
	Total dust	Respirable dust	Total dust	Respirable dust
Raw clay	4.4	0.7	0.1	0.2
Drying	6.0	0.7	13.8	0.4
Crushing, screening	13.4	1.8	4.7	0.8
Raymond milling	23.0	2.0	11.9	1.1
Shipping, loading	9.4	2.7	9.6	2.6
Mining	0.6	0.1	3.1	0.4

^aTotal dust and respirable dust were measured in different samples.

^bFrom Gamble *et al.* (1986)

Attapulgite fibres were found in phosphate mine dust in Tunisia; no quantitative data were given (Sébastien *et al.*, 1984).

(c) Nonoccupational exposure

Attapulgite fibres have been found in some US water supplies (Millette *et al.*, 1983).

2.3 Analysis

The analysis of clays, soils and dusts for the presence of attapulgite may require the use of both X-ray diffractometry and electron microscopy. Most attapulgite fibres have a diameter below the resolution limit of the light microscope (Bignon *et al.*, 1980; Zumwalde,

1976). In X-ray powder diffraction analysis, the strongest line at 1.05 nm is best suited for identification (Christ *et al.*, 1969; Keller, 1979).

Single fibres may be visualized and characterized by means of transmission or scanning electron microscopy. Selected area electron diffraction or X-ray microanalysis of the characteristic Mg, Al, Si and Fe contents can confirm the identity of attapulgite particles (Zumwalde, 1976; Bignon *et al.*, 1980).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals¹

(a) Intraperitoneal administration

Rat: Groups of 40 female Wistar rats, eight to 12 weeks of age, received three intraperitoneal injections of 25 mg attapulgite (30% of fibres >5 µm in length) [origin and purity unspecified] at one-week intervals, or other fibrous and granular dusts, suspended in 2 ml saline. Average survival time for rats given attapulgite was 46 weeks after the first injection. Of the 34 rats treated with attapulgite and necropsied, 26 (77%) had developed malignant tumours of the abdominal cavity (24 diagnosed as mesotheliomas and two as sarcomas). In similar groups of 40 female rats receiving a single injection of 6.25 or 25 mg UICC chrysotile from Zimbabwe, 27/35 and 25/31 developed malignant tumours of the abdominal cavity, respectively. No abdominal tumour was observed in 72 rats in a saline-control group. The abdominal tumour incidence in seven groups of about 40 rats each receiving four injections of 25 mg of different types of granular dust (actinolite, haematite, biotite, pectolite, sanidine or talc) ranged between 0 and 3% (one mesothelioma with talc, one spindle-cell sarcoma with sanidine and one carcinoma with pectolite) (Pott *et al.*, 1976).

(b) Intrapleural administration

Rat: Two groups of 30-50 female Osborne-Mendel rats, 12-20 weeks of age, received a single application of one of two attapulgite samples (obtained from sources in Attapulgus, GA, USA; considered to be refined; as verified by electron microscopy, composed entirely of short fibres of small diameter; >90% pure), uniformly dispersed in hardened gelatin, directly on the left pleural surface by open thoracotomy. One sample of attapulgite contained no fibres >4 µm in length; in the other, <1% of fibres counted were >4 µm. The rats were followed for two years and the survivors were then killed. Two pleural sarcomas were seen among 29 rats in each of the two attapulgite-treated groups. The incidences of pleural sarcomas were 3/491 in untreated rats and 17/615 in rats receiving pleural implants

¹The Working Group was aware of one completed but unpublished study and of one study in progress on the carcinogenicity of attapulgite administered by intraperitoneal injection to rats (IARC, 1986).

of ‘nonfibrous materials’ described by the authors as ‘noncarcinogenic’. In a group treated with UICC crocidolite, 14/29 rats developed pleural mesotheliomas (Stanton *et al.*, 1981).

In a preliminary report, it was stated that four groups of 40 Fischer 344 rats [age and sex unspecified] were given a single intrapleural injection of 20 mg Spanish attapulgite (either ultrasonicated or not) or UICC chrysotile B in 0.4 ml saline or saline alone. Less than 2% of attapulgite fibres in each sample were $>4 \mu\text{m}$ in length and $<0.2 \mu\text{m}$ in diameter. Interim evaluations [time unspecified] showed pleural mesotheliomas in dead animals: 10/24 treated with attapulgite without ultrasonication, 5/18 treated with attapulgite with ultrasonication, 9/21 treated with chrysotile B and 0/16 saline control animals (Wagner, 1982). [The Working Group noted that the results were preliminary and inadequately reported and that a number of animals were still alive at the time of reporting.]

[The Working Group noted that specimens of mineral dust used in experimental studies are frequently characterized for the presence or absence of a size or type of particle or fibre thought to have important biological properties. Most commonly, the percentage of the particle occurring in an aliquot is cited. However, without a denominator — the absolute number of particles or fibres per aliquot — it is impossible to compare fibre concentrations in different specimens.]

3.2 Other relevant biological data

(a) Experimental systems

Toxic effects

Minimal histological tissue damage was observed in Fischer 344 rats exposed to Spanish attapulgite [dose unspecified] by inhalation for up to 12 months; the fibrosis grade was approximately 3.0, which was similar to that observed with crocidolite (Wagner, 1982).

Woodworth *et al.* (1983) observed squamous metaplasia of Syrian hamster tracheal organ cultures exposed to 4 and 16 mg/ml [*sic*] attapulgite (fibre length, $\leq 5 \mu\text{m}$). The statistical significance of this observation was not established, while crocidolite (1-8 mg/ml) induced a significant effect.

At concentrations of $\geq 0.05 \text{ mg/ml}$, attapulgite was haemolytic to red blood cells from sheep (Schnitzer & Pundsack, 1970; Harvey *et al.*, 1984), rats (Koshi *et al.*, 1968), cattle (Oscarson *et al.*, 1986) and humans (Jaurand *et al.*, 1979).

Attapulgite was found to be toxic to Swiss T.0. mouse peritoneal macrophages, using release of cytoplasmic lactate dehydrogenase as the endpoint. Following treatment with 150 $\mu\text{g}/\text{ml}$ for 18 h, ‘short-fibred’ attapulgite [fibre dimensions not given] released more of the enzyme than ‘long-fibred’ attapulgite (Chamberlain *et al.*, 1982).

In glycogen-stimulated rat peritoneal macrophages treated with three samples (two from Japan and one from Georgia, USA) of 1 mg/ml attapulgite [fibre length unspecified], the intracellular acid phosphatase level was increased and lactic acid production was lowered, indicating cytotoxicity (Koshi *et al.*, 1968).

Attapulgite was toxic to P388D₁ macrophage-derived mouse cells (endpoint, trypan blue exclusion). Cells were treated for 4 h with 1 mg/ml attapulgite [type and dimensions

unspecified] (Harvey *et al.*, 1984) or for 48 h with 20 or 80 µg/ml Florida attapulgite (fibre length, < 2.5 µm) (Gormley & Addison, 1983). Using a different assay, Lewis and Lipkin (1985) reported no growth inhibition after treatment of P388D₁ cells with either 100 µg/ml of French or US attapulgite (maximum length, 1.2 µm and 1.6 µm, respectively) as determined by cell counting from photographs.

'Short-fibre' attapulgite did not induce giant-cell formation in human lung carcinoma cells (A549) treated for five days with 200 µg/ml. Colony formation of Chinese hamster lung fibroblasts (V79-4) was not modified following incubation for six days with 'several concentrations' of 'short fibres'. However, when the cells were treated with 'long fibres' (52 µg/ml), colony efficiency was reduced by 50% (Chamberlain *et al.*, 1982) [fibre dimensions not given]. Colony formation in human embryo intestinal cells (I-407) was not modified after treatment with 0.001-1 mg/ml US attapulgite from Georgia (length, generally < 2 µm), but was reduced with higher doses (35% reduction with 2.5 mg/ml and 43% with 5.0 mg/ml) (Reiss *et al.*, 1980).

Attapulgite (average fibre length, 0.8 µm) was not toxic to primary cultures of rat hepatocytes treated with concentrations of 1 or 10 µg/ml (endpoint, release of cytoplasmic lactate dehydrogenase) (Denizeau *et al.*, 1985).

Effects on reproduction and prenatal toxicity

Doses of 0.001 and 1.0 mg attapulgite clay were injected into the amnion of 107 white Leghorn chicken eggs. Of the 56 embryos that survived to the 12th day of incubation, 26 showed encephalocele or eyelid defects and, at the higher dose, severe twisting and distortion of the body axis and appendages. Similar effects were observed with other particulates such as sand, alumina and glass, but not in controls injected with saline (Williamson *et al.*, 1963).

Deposition, clearance and retention

Rats were exposed to experimentally generated aerosols of attapulgite [concentration and exposure schedule unspecified] in which dust particles were described as compact conglomerates of nonfibrous materials. However, discrete fibres were found in the lungs of animals examined after 18 months, indicating deagglomeration (Griffiths & Hill, 1983).

Mutagenicity and other short-term tests

At concentrations of up to 10 µg/ml, attapulgite (average fibre length, 0.8 µm) did not induce unscheduled DNA synthesis in primary cultures of rat hepatocytes (Denizeau *et al.*, 1985). At 10 and 20 µg/ml, attapulgite (from Senegal; fibre length, < 4 µm) did not induce sister chromatid exchanges *in vitro* in rat pleural mesothelial cells, while crocidolite did (Achard *et al.*, 1986).

(b) Humans

Toxic effects

Radiographs and pulmonary function measurements were taken in the course of routine surveillance by two companies in Georgia and Florida, USA, of 701 workers mining and

milling attapulgite clay (Gamble *et al.*, 1986). [Exposure data are reported in section 2.2(b).] The average tenure of employment was 11 years. The overall prevalence of pneumoconiosis ($\geq 1/0$ in the 1980 ILO classification) was 6.4%; 26 of 45 cases were category 1/0; 13, category 1/1 or 1/2; and five, category 2. Of the 45 cases of category 1/0, 16 had irregular opacities and 29 had rounded opacities. The prevalences of unilateral and bilateral pleural thickening were 3.2% and 4.2%, respectively. [The Working Group noted that in other studies conducted by the same group of investigators, the prevalence of bilateral pleural thickening was 7.9% in talc miners (in Montana, Texas and North Carolina, USA); 0.2% in potash workers in New Mexico, USA; and 0.4% in blue-collar workers in North Carolina, USA (Attfield *et al.*, 1982; Gamble *et al.*, 1982).] The prevalence of radiographic changes increased consistently (but not statistically significantly) with age and with cumulative exposure to dust, such that the prevalence of pneumoconiosis among workers exposed for more than 15 years was 11.9% in one company and 25.3% in the other; these results were adjusted for age, race and smoking habits. Forced expiratory volume in one second (FEV₁) was reduced among workers in one company in relation to cumulative exposure to total dust only. There was no consistent association of the prevalence of respiratory symptoms (cough, dyspnoea, wheezing) with tenure of employment or with cumulative dust exposure.

Effects on reproduction and prenatal toxicity

No data were available to the Working Group.

Deposition, clearance and retention

Using transmission electron microscopy, attapulgite fibres (42 000 fibres/ml) were observed in the lavage fluid of a patient with lung fibrosis who had been exposed occupationally to attapulgite for three years (Bignon *et al.*, 1980).

Attapulgite fibres (300 000 fibres/ml) were found in the urine of a 60-year-old woman who had ingested 6–9 g per day for six months of an attapulgite-containing drug, indicating that attapulgite passes through the gastrointestinal mucosa (Bignon *et al.*, 1980).

Mutagenicity and chromosomal effects

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity to humans

A cohort of 2302 men employed for at least one month between 1940 and 1975 at an attapulgite mining and milling facility in Georgia-Florida, USA, were followed through 1975 (Waxweiler *et al.*, 1986). [Exposure data are reported in section 2.2(b).] Among cohort members successfully traced, 317 had died compared to 388.1 expected based on age-, calendar year- and race-specific rates for US males. A significant deficit of mortality due to nonmalignant respiratory disease was observed (nine observed, 20.8 expected; standardized mortality ratio (SMR), 43; 90% confidence interval (CI), 23–76). A marked deficit of mortality from nonmalignant respiratory disease was seen, regardless of estimated dust exposure level, induction-latent period or duration of employment. A statistically significant excess of mortality due to lung cancer was observed among white men

ATTAPULGITE

169

(16 observed, 8.3 expected; SMR, 193; 90% CI, 121-293); but a deficit occurred among non-whites (five observed, 9.4 expected; SMR, 53; 90% CI, 21-112). Mortality from lung cancer in Georgia is lower than the national average for blacks and similar to national rates for whites (Mason *et al.*, 1975, 1976). Lung cancer risk was not associated significantly with cumulative dust exposure level, induction-latent period or duration of employment in men of either race, except that among those workers employed for at least five years in high-exposure jobs, five lung cancer deaths were observed *versus* 1.62 expected (SMR, 309; 90% CI, 122-649). Data on past smoking habits were not available.

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Attapulgite occurs in sedimentary clay strata and in arid and semi-arid climates around the world. Occupational exposure to attapulgite fibres occurs during the mining, milling, production and use of attapulgite, and in certain other mining operations. Consumer exposure occurs through use of dusty products such as pet litters and pharmaceutical preparations.

4.2 Experimental data

Attapulgite samples from different deposits were tested for carcinogenicity in rats in one experiment by intraperitoneal injection and in two experiments by intrapleural application. An attapulgite sample with 30% of fibres longer than 5 µm produced mesotheliomas and sarcomas in the abdominal cavity following intraperitoneal injection. In addition, one sample of attapulgite with less than 2% of fibres longer than 4 µm was reported to induce mesothelial tumours following intrapleural administration. Two samples of another attapulgite with less than 1% of fibres longer than 4 µm did not cause a significant increase in the incidence of tumours following intrapleural administration.

No data were available to evaluate the reproductive or prenatal toxicity of attapulgite to experimental animals.

Attapulgite did not induce unscheduled DNA synthesis in primary cultures of rat hepatocytes or sister chromatid exchanges in rat mesothelial cells.

4.3 Human data

Long-term occupational exposure to attapulgite was associated in the only available study with an exposure-related increase in the prevalence of pneumoconiosis.

A single epidemiological study of attapulgite miners and millers showed increased mortality from lung cancer among the small group with long-term, high-level exposure; data on past cigarette smoking habits were not available.

Overall assessment of data from short-term tests: Attapulgite^a

Genetic activity	Cell transformation		
	DNA damage	Mutation	Chromosomal effects
Prokaryotes			
Fungi/Green plants			
Insects			
Mammalian cells (<i>in vitro</i>)	—	—	
Mammals (<i>in vivo</i>)			
Humans (<i>in vivo</i>)			
Degree of evidence in short-term tests for genetic activity: Inadequate	Cell transformation: No data		

^aThe groups into which the table is divided and the symbol ‘—’ are defined on pp. 19-20 of the Preamble; the degrees of evidence are defined on pp. 20-21.

4.4 Evaluation¹

There is *limited evidence* for the carcinogenicity of attapulgite to experimental animals.
There is *inadequate evidence* for the carcinogenicity of attapulgite to humans.

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¹For definitions of the italicized terms, see Preamble, pp. 18 and 22.

ATTAPULGITE

171

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SEPIOLITE

1. Chemical and Physical Data

1.1 Synonyms and trade names

CAS Registry Nos: 18307-23-8, 15501-74-3

Chem. Abstr. Name: Sepiolite

Synonym: Meerschaum

1.2 Structure of typical mineral

Molecular formula: $\text{Mg}_2\text{Si}_3\text{O}_8 \cdot 2\text{H}_2\text{O}$

Sepiolite belongs to the clay family known as sepiolite-palygorskite. Its structure can be considered in some degree to be transitional between the structures of the chain and layered silicates which most clay minerals possess (Alvarez, 1984; Harben & Bates, 1984). Individual crystals are composed of sheet silicate units which consist of layers of SiO_4 tetrahedra with two such sheets orientated so that unshared oxygen atoms face each other. These are bonded together with magnesium atoms coordinated octahedrally between the individual unit chains. The units develop indefinitely along the 'c' axis of the crystal to produce a 'triple chain' of SiO_4 tetrahedra. In the 'b' direction of the crystal, the structural units are separated by a distance of one chain width; in the 'a' direction, these layers are developed and offset with respect to the layer above and below (Roberts *et al.*, 1974; Alvarez, 1984). The structure formed is orthorhombic, with cell parameters of $a = 1.35$, $b = 2.70$ and $c = 0.53$ nm (Brindley, 1959). This structural arrangement results in long, very thin, lath-like crystals which are similar in size to chrysotile asbestos fibrils. Sepiolite laths or fibres are usually combined to form either dense or spongy masses; the latter are often very light and gave the mineral its original German name of *meerschaum* (sea-foam) (Buie, 1983; Alvarez, 1984).

1.3 Chemical and physical properties

From Roberts *et al.* (1974) and Alvarez (1984), unless otherwise specified

- (a) *Hardness:* 2-2.5 on Mohs' scale
- (b) *Density:* ~ 2

- (c) *Cleavage:* Not determined
- (d) *Colour:* White with tints of grey-green or red; also light-yellow
- (e) *Description:* Similar to attapulgite but with an additional SiO_4 tetrahedron at regular intervals on the chain so that the unit cell is about 50% larger than that of attapulgite (Harben & Bates, 1984); usually clay-like, nodular and fibrous; also compact massive (meerschaum) or leathery (mountain skin) (Roberts *et al.*, 1974; Renjun, 1984).

1.4 Technical products and impurities

Sepiolite has an ideal theoretical composition of 55.65% SiO_2 , 24.89% MgO and 19.46% H_2O (Otsuka, 1984). It is often associated with other clays, such as attapulgite and montmorillonite (Anon., 1978), and non-clay minerals such as carbonates, quartz, feldspar and phosphates (Alvarez, 1984). The composition reported in two countries is presented in Table 1.

Table 1. Elemental composition (%) of sepiolite

Component	Spain ^a (4 deposits)	Japan ^b (10 deposits)
SiO_2	59-63	46-55
TiO_2	NA ^c	traces-0.2
Al_2O_3	1-4	0.1-5.5
$\text{Fe}_2\text{O}_3 + \text{FeO}$	0.3-0.9	0.05-11
MnO	NA	<0.01-3
MgO	21-24	13-24
NiO	NA	0.06-8
CaO	0.4-0.5	traces-0.8
$\text{Na}_2\text{O} + \text{K}_2\text{O}$	0.3-2	0.03-4
H_2O	11-13	17-29

^aFrom Galan & Castillo (1984)

^bFrom Otsuka (1984)

^cNot available

The world's largest supplier of sepiolite sells granules 75 and >95% pure in many grades, the most important of which is the 6/30 mesh grade, used for absorbents. Finer grades, namely 30/60, 60/100, 120/400 and 400 mesh, are used as pesticide carriers, in animal feed and in bleaching applications. The high-purity materials (>95% pure) are normally marketed as catalysts and in rheological applications (Clarke, 1985). The major mineral contaminant of Spanish sepiolite products is montmorillonite (Anon., 1978); the following minerals are minor contaminants: illite, attapulgite, calcite, smectite, dolomite, quartz, cristobalite and feldspars (Galan & Castillo, 1984).

Sepiolite is marketed as meerschaum in block form (Buie, 1983). Turkish meerschaum exported to the USA is shipped in 20-kg blocks (Ampian, 1984).

2. Production, Use, Occurrence and Analysis

2.1 Production

(a) Production

Sepiolite and sodium sepiolite (loughlinite) have been classed with attapulgite among the hormitic clays (Anon., 1978). Sepiolite is structurally and functionally very similar to attapulgite and often occurs in association with this and other clay minerals. Sepiolite may have been described geologically only in 1758, but it has been used in nearly pure form for many hundreds of years in the Mediterranean basin for carving pipes and making pottery (Alvarez, 1984). Commercial production of sepiolite in Spain began in 1945 (Galan & Castillo, 1984).

The material from which carved items are produced is known as meerschaum, and, until recently, this was the term used to describe the commercially available, highly pure, compact form of sepiolite. As larger sepiolite deposits became known and other specific applications for sepiolite were developed, a dual nomenclature system arose. 'Sepiolite' came to be used for the industrial mineral, including both compact and earthy varieties, and 'meerschaum' for the specialty mineral (Buie, 1983).

Most production occurs in three countries — Spain, the USA and Turkey, the first accounting for over 90% of world production (Clarke, 1985). Meerschaum has been mined on a very small scale and somewhat sporadically in France, India, the Islamic Republic of Iran, Kenya, Somalia and the United Republic of Tanzania (Buie, 1983). Sepiolite has been found rarely in the USSR and is probably not mined in that country (Ovcharenko & Kukovsky, 1984).

Sepiolite is mined and marketed similarly to attapulgite, although less processing is required for the production of commercial grades. The large Spanish operation produces high-purity sepiolite and sepiolite-montmorillonite mixtures in various grades (Anon., 1978). Production was 203 000 tonnes in 1979 and 375 000 tonnes in 1984 (British Geological Survey, 1985; Clarke, 1985).

US production is controlled by one company, which has a capacity of 40 000 tonnes per year but produces much less (Clarke, 1985). Turkish production of industrial sepiolite grades is probably minor, but 3-31 tonnes of crude or block meerschaum were produced annually in the 1970s (Buie, 1983) and about 6 tonnes in 1984 (Ampian, 1984). US imports of block meerschaum, from Somali, Tanzanian and Turkish mines, ranged from 0.7 to 6.3 tonnes in the years 1978-1983 (Ampian, 1980, 1982, 1984).

(b) Use

In 1984, 85% of high-purity Spanish sepiolite was used as absorbents; most of the remainder was used in animal feeds (7.5%) and as pesticide carriers (4%). Pet litter absorbent is the most important single product, but sepiolite is also used as a decolourizer or bleaching agent in the production of vegetable and mineral oils. It is incorporated into

animal feeds as a feed binder and as a carrier for nutrients and growth promoters (Alvarez, 1984). In tonnages, uses in drilling muds and as industrial catalysts are of minor significance (Alvarez, 1984; Clarke, 1985).

Sepiolite is also used in anticaking agents, cosmetics, cigarette filters, detergents and pharmaceutical products (Alvarez, 1984).

Meerschaum is almost exclusively carved into pipes and cigarette holders (Buie, 1983; Ampian, 1984).

2.2 Occurrence

(a) *Natural occurrence*

Both sepiolite and meerschaum are found in sedimentary strata, in arid and semi-arid climates around the world (Callen, 1984). Significant deposits of sepiolite have been reported in China, Japan, Madagascar, the Republic of Korea, Spain, Turkey, the United Republic of Tanzania and the USA (Alvarez, 1984; Callen, 1984, Renjun, 1984; Clarke, 1985).

Sepiolite deposits that are exploited commercially occur in sedimentary formations that are believed to have formed under lacustrine conditions in fairly arid climates (Callen, 1984).

(b) *Occupational exposure*

Occupational exposure occurs during mining, milling and production of sepiolite, however, no data on exposure measurements at workplaces were available to the Working Group.

(c) *Nonoccupational exposure*

Sepiolite fibres were detected in the soil in an agricultural area of southern Bulgaria (Burilkov & Michailova, 1970).

2.3 Analysis

The analysis of clays, soils and dusts for the presence of sepiolite may require the use of both X-ray diffraction and electron microscopy. Most sepiolite fibres have a diameter below the resolution limit of the light microscope (Alvarez, 1984).

The crystallinity of sepiolite samples may vary considerably, but the strongest 1.21 nm line in an X-ray powder diffraction pattern is best suited for identification (Brindley, 1959; Keller, 1979).

Single fibres may be visualized and characterized by means of transmission or scanning electron microscopy. Selected area electron diffraction or X-ray microanalysis for the characteristic Mg:Si ratio can confirm the mineralogical identity of sepiolite particles (Brindley, 1959; Galan & Castillo, 1984; Rödelsperger *et al.*, 1985).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

Intrapleural administration

Rat: In a preliminary report, it was stated that five groups of 40 Fischer 344 rats [age and sex unspecified] were given a single intrapleural injection of 20 mg of three samples of Spanish sepiolite (two from the mine site, one ultrasonicated, the other not and one of pure commercial grade 00), or chrysotile B asbestos, in 0.4 ml saline or saline alone. The sepiolite samples contained no fibres >5 µm in length. Interim evaluations [time unspecified] showed no pleural mesothelioma in rats exposed to sepiolite (ultrasonicated, 0/21; not ultrasonicated, 0/21; commercial-grade, 0/9) or saline alone (0/16), but mesotheliomas occurred in 9/12 chrysotile B-exposed rats that died (Wagner, 1982). [The Working Group noted that the results could not be evaluated, because a large number of animals were still alive at the time of the report.]

3.2 Other relevant biological data

(a) *Experimental systems*

Toxic effects

Minimal histological tissue damage was observed in Fischer 344 rats exposed to sepiolite [dose unspecified] by inhalation for up to 12 months; the fibrosis grade was approximately 3.0, which was similar to that observed with crocidolite (Wagner, 1982).

Sepiolite (>10 mg/ml) was haemolytic to sheep red blood cells (Schnitzer & Pundsack, 1970; Wright *et al.*, 1980). Short sepiolite fibres (90% <2 µm in length) were not toxic to Swiss T.0. mouse peritoneal macrophages, but longer fibres (90% <4 µm in length) induced the release of cytoplasmic lactate dehydrogenase following treatment with 150 µg/ml for 18 h (Chamberlain *et al.*, 1982).

In glycogen-stimulated rat peritoneal macrophages treated with five samples of 1 mg/ml sepiolite (three from Japan, one from Spain and one from Canada), the acid phosphatase level was increased and lactic acid production was lowered, indicating cytotoxicity (Koshi *et al.*, 1968).

In assays using P388D₁ macrophage-derived mouse cells treated for 48 h, 10 µg/ml sepiolite [fibre length not specified] was not toxic (endpoints, trypan blue exclusion and enzyme levels), while 50 µg/ml induced measurable cell injury (Wright *et al.*, 1980).

'Short-fibre' (90% <2 µm in length) sepiolite did not induce giant-cell formation in human lung carcinoma cells (A549) treated for five days with 200 µg/ml, but treatment with 'long-fibre' (90% <4 µm in length) sepiolite resulted in 25% giant-cell formation (untreated control, 3%). Colony formation was not modified in Chinese hamster lung fibroblasts (V79-4) incubated for six days with several concentrations (≥ 100 µg/ml) of 'short fibres',

whereas 'long fibres' (85 µg/ml) reduced colony-forming efficiency by 50% (Chamberlain *et al.*, 1982).

Sepiolite (average fibre length, 2 µm) was not toxic to primary cultures of rat hepatocytes treated with 1 or 10 µg/ml (endpoint, release of cytoplasmic lactate dehydrogenase) (Denizeau *et al.*, 1985).

Effects on reproduction and prenatal toxicity

No data were available to the Working Group.

Deposition, clearance and retention

Rats were exposed to experimentally generated aerosols of sepiolite [concentration and exposure schedule unspecified] in which dust particles were described as compact conglomerates of nonfibrous materials. However, discrete fibres were found in the lungs of animals examined after 18 months, indicating deagglomeration (Griffiths & Hill, 1983).

Mutagenicity and other short-term tests

Concentrations of up to 10 µg/ml sepiolite (average fibre length, 2 µm) did not induce unscheduled DNA synthesis in primary cultures of rat hepatocytes (Denizeau *et al.*, 1985).

(b) Humans

Toxic effects

Clinical and radiological evidence of pulmonary fibrosis (small irregular opacities) was encountered in 10/63 sepiolite trimmers in Eskisehir, Turkey. Radiological examination of inhabitants of four villages near Eskisehir, where sepiolite has been mined and processed for more than 100 years, showed no evidence of pleural disease (Baris *et al.*, 1980).

Effects on reproduction and prenatal toxicity

No data were available to the Working Group.

Deposition, clearance and retention

No data were available to the Working Group.

Mutagenicity and chromosomal effects

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity to humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Sepiolite occurs in sedimentary clay strata in arid and semi-arid climates around the world. Occupational exposures occur during mining, milling, production and use of

sepiolite, and in certain other mining operations. Consumer exposure occurs through use of dusty products such as pet litters.

4.2 Experimental data

No adequate data on the carcinogenicity of sepiolite to experimental animals were available to the Working Group.

No data were available to evaluate the reproductive or prenatal toxicity of sepiolite to experimental animals.

Sepiolite did not induce unscheduled DNA synthesis in primary cultures of rat hepatocytes.

Overall assessment of data from short-term tests: Sepiolite^a

	Genetic activity			Cell transformation
	DNA damage	Mutation	Chromosomal effects	
Prokaryotes				
Fungi/Green plants				
Insects				
Mammalian cells (<i>in vitro</i>)	—			
Mammals (<i>in vivo</i>)				
Humans (<i>in vivo</i>)				
Degree of evidence in short-term tests for genetic activity: Inadequate				Cell transformation: No data

^aThe groups into which the table is divided and the symbol ‘—’ are defined on pp. 19-20 of the Preamble; the degrees of evidence are defined on pp. 20-21.

4.3 Human data

Pulmonary opacities were reported in one group of sepiolite workers.

No data were available on the carcinogenicity of sepiolite to humans.

4.4 Evaluation¹

There is *inadequate evidence* for the carcinogenicity of sepiolite to experimental animals.

No data were available to evaluate the carcinogenicity of sepiolite to humans.

¹For definition of the italicized term, see Preamble, p. 18.

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SEPIOLITE

183

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TALC

1. Chemical and Physical Data

1.1 Synonyms and trade names

CAS Registry No.: 14807-96-6

Chem. Abstr. Name: Talc

Synonyms¹: Soapstone; steatite; talcum

Trade names¹: Agalite; Asbestine; B9 Finntalc P40; B13; B13 (mineral); Beaver White 200; CP 10-40; CP 38-33; Crystalite CR 6002; Desertalc 57; Emtal 500; Emtal 549; Emtal 596; Emtal 599; Fibrene C 400; French Chalk; FW-XO; HSDB 830; IT Extra; LMR 100; Microneeca K1; Micro White 5000A; Microtalco IT Extra; Mistron; MP 25-38; MP 40-27; MP 45-26; MST; MT 12-50; Mussolini; NCI-CO6018; Nytal 200; Nytal 400; Pk-C; Pk-N; Polytal 4641; Polytal 4725; Potstone; Snowgoose; Steawhite; Supreme; Supreme dense; Talcan PK-P; Talcron CP 44-31

1.2 Structure of typical mineral

Molecular formula: $\text{Mg}_3\text{Si}_4\text{O}_{10}(\text{OH})_2$

The original X-ray spectra of talc (Gruner, 1934; Hendricks, 1938) indicated that the mineral had a monoclinic structure. Later investigations (Rayner & Brown, 1966; Ross *et al.*, 1968) demonstrated that many if not all talcs are triclinic (Table 1). The basis of the talc structure is characterized by a hexagonal sheet arrangement of SiO_4 tetrahedral groups linked in a common plane. Each SiO_4 tetrahedron shares three planar oxygen atoms with its neighbouring tetrahedra; the fourth oxygen, the apex of the tetrahedron, is not shared. Two such sheets are orientated so that unshared apical oxygen atoms face each other. The sheets are bonded by magnesium atoms, which are coordinated by two oxygens and one hydroxyl group from each sheet, which form a brucite layer. This structural arrangement results in a double-sheet structure in which the valency demands of the constituent atoms are completely satisfied. Crystals of talc are made up of stacks of these double-sheet units held together by the weakest of chemical bonds — the Van der Waal's forces. As the individual sheets cannot be bonded together, they can be separated by slight forces, causing slippage of the individual sheets along a perfect cleavage direction in the basal plane (Rohl *et al.*, 1976; Pooley & Rowlands, 1977).

¹These synonyms and trade names cover talc, talc-containing materials and talc contaminated with other minerals as admixtures.

Table 1. Lattice parameters and crystallographic axes of talc

Lattice parameters (nm)			Crystallographic axes			System	Reference
a	b	c	α	β	γ		
0.526	0.910	1.881	90°00'	100°00'	90°00'	Monoclinic	Gruner (1934)
0.527	0.913	1.888	90°00'	100°15'	90°00'	Monoclinic	Hendricks (1938)
0.528	0.915	1.89	90°00'	100°15'	90°00'	Monoclinic	Roberts <i>et al.</i> (1974)
0.5255	0.9137	0.9448	90°46'	98°55'	90°00'	Triclinic	Ross <i>et al.</i> (1968)
0.5293	0.9179	0.9496	90°57'	98°91'	90°03'	Triclinic	Ross (1984)

1.3 Chemical and physical properties

From Roberts *et al.* (1974)

- (a) *Hardness:* 1 on Mohs' scale
- (b) *Density:* 2.58-2.83
- (c) *Cleavage:* (001) perfect
- (d) *Colour:* Pale-green to dark-green or greenish-grey; also white, silvery-white, grey, brownish; translucent; pearly, greasy or dull
- (e) *Description:* Commonly thin tabular crystals, up to 1 cm in width. Usually massive, fine-grained, compact; also as foliated or fibrous masses or in globular stellate groups

1.4 Technical products and impurities

The chemistry of talc shows little variation, indicating that only a limited substitution of ions takes place in the mineral lattice. When expressed in the standard oxide form, the ideal chemical composition is: 31.7% MgO, 63.5% SiO₂, 4.8% H₂O (Pooley & Rowlands, 1977). Small amounts of aluminium and titanium may substitute to some extent for silicon, and it is common to find iron, nickel, manganese or chromium substituting to some extent for magnesium. Iron and nickel substitute for magnesium in the greatest amounts (Pooley & Rowlands, 1977), and a talc with almost complete substitution of magnesium by iron, called minnesotaite, is abundant in the iron formations of Minnesota, USA (Deer *et al.*, 1971). One major talc deposit in the eastern USA contains substantial amounts of nickel — up to 0.2% (Rohl *et al.*, 1976). Nickel-substituted talcs are also associated with serpentine bodies, at up to 0.5% by weight (Pooley & Rowlands, 1977). Table 2 gives examples of the mineral composition of talcs (Deer *et al.*, 1971).

Table 2. Bulk chemical analysis of talcs (%)^a

Component	Talc ^b								
	1	2	3	4	5	6	7	8	9
SiO ₂	62.61	62.67	62.47	62.16	60.06	60.02	60.88	61.07	51.29
TiO ₂	—	—	—	—	—	—	0.10	—	0.04
Al ₂ O ₃	—	0.38	0.47	0.88	1.60	1.88	1.98	2.42	0.61
Fe ₂ O ₃	—	0.68	—	—	—	—	0.83	1.49	2.00
FeO	2.46	0.65	0.79	1.41	1.74	1.51	—	—	33.66
MnO	0.01	—	0.00	—	—	—	—	—	0.12
MgO	30.22	29.95	31.76	30.86	30.83	30.39	31.18	29.13	6.26
CaO	—	1.35	0.00	—	0.40	1.00	0.14	0.75	0.00
Na ₂ O	—	—	—	—	—	—	—	—	0.08
K ₂ O	—	—	—	—	—	—	—	—	0.03
H ₂ O ⁺	4.72	5.05	4.70	4.92	5.02	5.37	4.98	4.82	5.54
H ₂ O ⁻	—	—	0.06	—	—	0.32	—	—	0.24

^aFrom Deer *et al.* (1971)^b1, talc, altered periodotite, Muruhatten, northern Sweden; 2, talc, Shabrov, Urals, USSR; 3, talc, Murphy, North Carolina, USA; 4, light-green talc, Malangen, Norway; 5, green talc, altered serpentine, Parma district, Appenines, Italy; 6, black talc, with carbonaceous material derived from a bluish-grey rock, Parma, Appenines, Italy; 7, talc, Mount Fitton, South Australia; 8, talc, altered tremolite, Yellandu Warangal district, Hyderabad, India; 9, greenish-grey iron talc (minnesotaite), East Mesabi range, Minnesota, USA

Since talc is formed by alteration or metamorphosis of rocks, it is found associated with many types of minerals. Rohl *et al.* (1976) listed the following minerals as commonly occurring in talc deposits: calcite, dolomite, magnesite, tremolite, anthophyllite, antigorite, quartz, pyrophyllite, micas and chlorites. Chrysotile and lizardite were noted as 'uncommon' constituents. When mined, talc ore may contain several of the minerals noted in Table 3.

In one study of Vermont (USA) talc, the mined and milled ore contained 20-100% each of talc and magnesite, a small amount of chlorite (5-20%) and minor amounts (<5%) of dolomite, calcite, quartz, phlogopite and biotite (Boundy *et al.*, 1979). An analysis of samples of mined and milled talc from New York (USA) yielded the following concentrations of minerals: talc, 12-50%; tremolite, 30-55%; anthophyllite, 3-35%; serpentine, 1-8%; calcite, <1-4%; and quartz, <0.1-20% (Schepers & Durkan, 1955a). A more recent examination of talc from Texas (USA) showed the presence of fibrous tremolite and antigorite (Gamble *et al.*, 1982). Rohl *et al.* (1976) showed that some US talcum powders marketed prior to 1975 contained chlorite, phlogopite, calcite, dolomite, quartz, kaolin, tremolite, anthophyllite, chrysotile, pyrophyllite and rutile. One French talc (Luzenac 15MOO) has been reported to contain 90% talc, 8% chlorite, 1% dolomite and no asbestos fibre (Talcs de Luzenac, 1982). An Italian talc (grade 00000) was reported to contain 92% talc, 3% chlorite, 1% carbonates and 0.5-1% quartz and no tremolite or chrysotile asbestos (Wagner *et al.*, 1977).

Table 3. Minerals that occur commonly in talcs^a

Mineral group	Phase	Formula
Carbonates	Calcite	CaCO_3
	Dolomite	$\text{CaMg}(\text{CO}_3)_2$
	Magnesite	MgCO_3
Amphiboles	Tremolite ^b	$\text{Ca}_2\text{Mg}_5\text{Si}_8\text{O}_{22}(\text{OH})_2$
	Anthophyllite ^b	$(\text{FeMg})_7\text{Si}_8\text{O}_{22}(\text{OH})_2$
Serpentine	Antigorite	$\text{Mg}_3\text{Si}_2\text{O}_5(\text{OH})_4$
	Chrysotile (uncommon)	$\text{Mg}_3\text{Si}_2\text{O}_5(\text{OH})_4$
	Lizardite (uncommon)	$\text{Mg}_3\text{Si}_2\text{O}_5(\text{OH})_4$
Others	Quartz	SiO_2
	Mica, e.g., phlogopite	$\text{K}_2(\text{Mg},\text{Fe})_6[\text{Si}_6\text{Al}_2\text{O}_{20}](\text{OH})_4$
	Chlorite, e.g., penninite	$(\text{Mg},\text{Al},\text{Fe})_{12}[(\text{Si},\text{Al})_8\text{O}_{20}](\text{OH})_{16}$
	Pyrophyllite	$\text{Al}_4[\text{Si}_8\text{O}_{20}](\text{OH})_4$

^aFrom Rohl *et al.* (1976)^bOccurring as nonasbestiform and asbestiform varieties

Technical products of talc are sold in a multitude of grades, which have functional or physical characteristics especially suited for certain applications. Clifton (1985) outlined the following guidelines for talc specifications by end use:

Ceramics: Uniform chemical and physical properties are required. Manganese and iron are usually objectionable. For high frequency insulators, no more than 0.5% calcium oxide, 1.5% iron oxide and 4% aluminium oxide can be tolerated.

Paints: Impurities that grind to colours other than white are highly objectionable. To yield the desired smooth paint film, at least 98.5% must pass through a 325-mesh screen.

Roofing: A low-grade, off-colour, impure talc is acceptable.

Insecticides: Requirements are chemical inertness with respect to toxicants, satisfactory bulk density and low abrasive characteristics.

Rubber: Many synthetic rubbers include ground talc as fillers in compounding formulations.

Cosmetics and pharmaceuticals: Talc must be grit free, finely sized, chemically pure and pleasing in colour. For cosmetics, talc must have good dry-slip characteristics.

Paper: Requirements include chemical inertness, softness, freedom from grit, satisfactory ink acceptance, brightness and dispersibility in water.

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(a) Production

Talc-containing rocks were first used in prehistoric times for utensils and ornaments (Roe & Olson, 1983); the term 'talc' was first applied to this mineral in 869 AD (Kuzvart, 1984). The abundance of talc and the facility with which it can be mined, combined with its many desirable functional properties, have made it an important industrial mineral. Mining of talc for commercial purposes probably began several hundred years ago when talc blocks were used for building materials and cooking utensils (Clifton, 1985).

The world reserve base of talc and the related aluminium silicate, pyrophyllite, is estimated to be 1200 million tonnes (Clifton, 1985; Table 4).

Table 4. Worldwide reserve base of talc and pyrophyllite^a

Region	Million tonnes
Africa	18
North America	580
South America	18
Asia and Oceania	362
Europe	172

^aFrom Clifton (1985); talc and pyrophyllite are not distinguished.

The first talc-grinding mill in the USA began operation in about 1880, suggesting the first large-scale US production of ground talc products. US production for many years continued to include both ground talc products and carved items (Clifton, 1985). 'Soapstone' blocks were first produced in open-pit operations, and the vast majority of world talc mining operations continue to rely on open-cast mining methods. Notable exceptions are in Austria and Italy, where necessity or the prospect of high-grade talc in deeper deposits has made underground mining an economically viable operation (Clarke, 1979). Talc sold in blocks is generally removed using hand tools; talc for grinding is mined by drilling and blasting methods (Clifton, 1985).

Practices for refining talc ores vary widely. In some operations, such as those of one mine in France, talc is initially sorted by hand to supply cosmetic talcs of different colour and physical characteristics (Clarke, 1979). Since most uses of talc have not required highly pure products, beneficiation and sophisticated milling and other processing techniques have not been used before shipping. Early talc mills were used to process both talc and cereal grains, the final product in both cases being a coarse powder (Roe & Olson, 1983).

The latest technology in talc refining employs flotation separation, drying of the filtered powder cake, and sizing or further grinding before shipping (Roe & Olson, 1983; Clifton, 1985). Flotation techniques are especially prevalent in North American, Norwegian and Finnish operations (Sinha, 1982).

Talc is mined in over 40 countries and is used in numerous manufacturing industries in over 60 countries (Roe & Olson, 1983; Harben & Bates, 1984). Commercial talc production figures in 1950-1983 are listed by region in Table 5.

Table 5. Talc production by world region, 1950-1983 (1000 tonnes)^a

Region/ country	Important producers	Year					
		1950	1960	1970	1980	1981	1982
Africa	Egypt, South Africa	8	9	14	14	11	18
Asia	China, Republic of Korea	7	181	354	1312	1280	1248
Australia		9	16	48	160	75	143
Europe	France, Italy, Austria, Finland, Norway	344	553	820	1180	1153	1195
India and Pakistan		25	95	161	379	380	348
Japan		12	50	138	148	120	106
North America	USA	475	585	891	1124	1218	1035
South America	Brazil, Argentina	13	50	118	380	376	354
USSR		—	250	380	490	500	510
							510

^aFrom Colonial Geological Surveys (1957); Institute of Geological Sciences (1967, 1978); British Geological Survey (1985). Figures are given for 'talc', although sometimes figures were not provided separately for talc production and pyrophyllite production.

Although the largest producers of talc are typically net exporters, notably Australia, Austria, China, France and the USA, several import talc in large quantities as well. Japan is by far the most important world market for talc, importing over 615 200 tonnes in 1983. Canada, the Federal Republic of Germany, Mexico, the UK, the USA and the USSR account for most of the remainder of talc imports (British Geological Survey, 1985).

(b) Use

Talc is one of the most versatile inorganic substances available to industry (Roe & Olson, 1983). Since its uses are dependent on the mineral character of the refined ore, more than many other industrial minerals, talc ores are often referred to by physical type, and used according to their functional characteristics. Although use patterns vary substantially from region to region, four major applications may be highlighted.

Ceramics

In the USA, 35%, and in Europe, nearly 10%, of native or imported talcs is used in ceramics (Anon., 1982; Clifton, 1985). Talc is especially useful in ceramics for its colour, fast-firing and low shrinkage properties. It has been used in floor- and wall-tiles, china, glazes, electrical porcelains, sanitary ware, kiln furniture and pottery (Clifton, 1985). Some china contains 15% talc by weight, while some pottery contains 40%. Up to 80% talc has been used in ceramic insulators (Roe & Olson, 1983).

Paper

The most important use of talc in Europe and Japan and the fastest-growing use in the USA is in the coating and filling of paper (Anon., 1982; Roe & Olson, 1983). The largest talc importer, Japan, uses 80% of its imports in the paper industry (Clarke, 1979). This statistic, combined with the 50% consumption pattern of talc for paper in Europe (Anon., 1982), makes this the predominant use of talc in the world (Clarke, 1979).

Plastics and building materials

In 1983, about 165 000 tonnes of talc were used in the plastics, rubber and roofing industries in the USA, representing 20% of the total consumption (Clifton, 1985). Talc has become an important component of many types of US plastics, as a stabilizer, reinforcer and filler used at up to 70% w/w. In roofing materials, talc is added at 10-35% to asphalt in composite shingling materials, to impart stability and weather resistance (Roe & Olson, 1983).

Paints

Approximately 15-25% of the talc used in most industrialized nations is as a pigment extender and filler in paints (Anon., 1982). As with the paper application, fineness of grade and colour are most important to the functional characteristics of the compound. US consumption of talc for use in paints was 213 000 tonnes in 1979 (Roe & Olson, 1983) and 150 000 tonnes in 1983 (Clifton, 1985).

Other uses

A significant, although less commercially important use of talc is in cosmetics. In the USA and Europe, approximately 5% of native and imported ores are used for this purpose (Anon., 1982; Clifton, 1985). Talc is directly available to consumers as facial cosmetics and talcum powders. US talcum powders marked prior to 1973 contained up to 95% by weight talc mineral; however, some commercial talcum powders contained no talc (e.g., starch was used). Mineral impurities such as amphibole minerals (tremolite, anthophyllite) and quartz were found in concentrations up to 14 and 35% by weight, respectively (Rohl *et al.*, 1976). Talc is also used as an excipient in pharmaceuticals and as a filler in toothpastes and soaps (Rohl & Langer, 1979; Kužvar, 1984).

Other uses of talc are as a cereal grain polisher (especially rice), as an ingredient in floor waxes and shoe polishes, as a carrier and diluent for pesticides, as a textile component, as an oil absorber, as a lubricant and in spackling and patching compounds (Rohl & Langer, 1979; Roe & Olson, 1983; Clifton, 1985).

(c) *Regulatory status and guidelines*

Occupational exposure limits in various countries are listed in Table 6.

Table 6. Occupational exposure limits for talc (mg/m³)^a

Country	Year	Total dust (mg/m ³)	Respirable dust (mg/m ³)
Australia	1978	2.5	
Czechoslovakia	1976	6	
Finland	1981	5 ^b	
France	1985		2 ^b
Italy	1978	5	1.6
Norway	1981	6	
United Kingdom	1985	10	1
USA			
ACGIH	1986		2 ^b
OSHA	1983	(20 mppcf) ^{b,c}	
USSR	1976	4	
Yugoslavia	1971	12	4

^aFrom International Labour Office (1980); Direktoratet för Arbeidstilsynet (1981); Työsuojeluhallitus (1981); US Occupational Safety and Health Administration (OSHA) (1983); Health and Safety Executive (1985); Institut National de Recherche et de Sécurité (1985); American Conference of Governmental Industrial Hygienists (ACGIH) (1986)

^bAsbestos fibre standards are used for fibrous forms

^cContaining <1% quartz

2.2 Occurrence

(a) *Natural occurrence*

Talc rocks are formed by several complex geological processes reacting upon many chemically diverse preexisting rock types. Hydrothermal alteration of magnesia- and silica-rich ultramafic rocks, under a range of low-to-moderate temperatures and pressures, may produce talc. Thermal metamorphism of silica-rich dolomite will also produce talc. These processes, however, also commonly result in the formation of a number of other coexisting mineral phases — predominantly hydrous magnesium silicates. Some of these — for example, anthophyllite, tremolite and serpentine minerals (including chrysotile) — may occur as microscopic intergrowths with talc, as macroscopic nodules, or even as discrete zones within or adjacent to talc. Talc rock is therefore often a mixture of minerals varying in kind and quantity (Rohl & Langer, 1974; Rohl *et al.*, 1976; Clifton, 1985).

Fibre intergrowths are often such that even extensive beneficiation may not yield a pure product. Thus, where fine-grained intergrowths of talc and tremolite occur, the processed product will probably contain residual tremolite (Rohl *et al.*, 1976).

(b) *Occupational exposure*

Talc-milling processes do not usually alter the mineral composition of the talc mixture delivered to the mill, but rather produce a talc with different physical properties dependent on particle size. Exposure to talc dust occurs during mining, crushing, separating, bagging, loading and in end-use facilities, such as rubber dusting and addition of talcs to ceramic clays and glazes. Since industrial talc is a mixture of various associated minerals, occupational exposure is to a mixture of mineral dusts.

Studies that provide information on occupational exposures to talc are summarized in Table 7 and described in more detail below. As with most industrial dust exposures, nearly all measurements made prior to approximately 1970 were done by collecting particles in an impinger and counting them by optical microscopy. Concentrations are thus expressed as millions of particles per cubic foot of air (mppcf).

In Georgia, USA, average dust exposures for miners using jackhammer drills were 1440 mppcf and those for millers 52 mppcf. The talc was reported to contain 45% tremolite and 45% talc, with little or no free silica (Dreessen, 1933). Average dust concentrations in a talc mine were reported to range from 32-855 mppcf (six samples), whereas average mill exposures ranged from 17-1672 mppcf (14 samples). The dust was reported to contain 70% talc, 20-30% dolomite and 10% tremolite, and no free silica except for occasional fragments; its morphology was described as 'bladed crystals'. Highest dust exposures were in bagging operations (Dreessen & DallaValle, 1935).

Occupational exposures to talc dust in mines and mills in New York State, USA, have been studied extensively (Siegal *et al.*, 1943; Kleinfeld *et al.*, 1955; Messite *et al.*, 1959; Kleinfeld *et al.*, 1967, 1974; Dement & Zumwalde, 1979; Dement *et al.*, 1980). Talc deposits in the state have been found to differ significantly in mineral composition, depending on location. Siegal *et al.* (1943) reported that talc produced in St Lawrence County contained tremolite, anthophyllite and only traces of quartz, and described the particle morphology as straight, needle-like fibres with a maximum length of 15 µm. Kleinfeld *et al.* (1973) also reported the major fibrous components of these talcs to be tremolite and anthophyllite, based on detailed electron microscopic observations. Bulk talc samples from another mine and mill in upper New York State were analysed for mineral content by optical petrographic microscopy, electron microscopy and X-ray diffraction. The mineral composition (by weight) of the talc bulk samples was 14-48% talc, 37-59% tremolite (including both fibrous and nonfibrous habits), 4.5-15% anthophyllite (including both fibrous and nonfibrous habits, 0.25-2.6% free silica, 0.0-1% calcite, 0.5-1% dolomite and 10-15% serpentines (largely lizardite and antigorite) (Dement & Zumwalde, 1979; Dement *et al.*, 1980).

Talc dust and fibre exposures in mining and milling operations in St Lawrence County, NY, for the period 1945-1972 are summarized in Table 8. Prior to dust control measures, such as wet drilling, average exposures to mine dust ranged from 120-818 mppcf; after 1945, these were reduced to 5-19 mppcf. Exposures in mills prior to 1945 ranged from 69-278 mppcf; average exposures in 1972 ranged from 7-36 mppcf. In 1972, optical fibre counts, using membrane-filter sampling and analyses, revealed that exposures in mines were low

Table 7. Studies of occupational exposures to talc

Reference	Industry studied	Location of talc deposit	Date of exposure measurements	Measurement method employed	Other minerals present in talc studied
Dreessen (1933)	Mining/ Milling	Georgia, USA	Pre 1933	Impinger	Tremolite
Dreessen & DallaValle (1935)	Mining/ Milling	Georgia, USA	Pre 1935	Impinger	Tremolite, dolomite
Siegal <i>et al.</i> (1943)	Mining	New York, USA	1940-1941	Impinger	Tremolite, anthophyllite, traces of free silica
Kleinfeld <i>et al.</i> (1955); Messite <i>et al.</i> (1959); Kleinfeld <i>et al.</i> (1967, 1974)	Mining/ Milling	New York, USA	Pre 1945-1972	Impinger	Tremolite, anthophyllite, carbonates, traces of free silica
Kleinfeld <i>et al.</i> (1973)	Mining/ Milling	New York, USA	1954-1970	Impinger, optical fibre counts	Tremolite, anthophyllite
Dement & Zumwalde (1979); Dement <i>et al.</i> (1980)	Mining/ Milling	New York, USA	1975	Gravimetric, optical and electron microscopy fibre counts	Tremolite, calcite, anthophyllite, dolomite, serpentines, silica
Rubino <i>et al.</i> (1976)	Mining/ Milling	Piedmont, Italy	1920-1975	Impinger	Small amounts of tremolite
Boundy <i>et al.</i> (1979)	Mining/ Milling	Vermont, USA	1975-1976	Optical and electron microscopy fibre counts	Dolomite, calcite, magnesite, chlorite, traces of other minerals
Greife (1980); Gamble <i>et al.</i> (1982)	Mining/ Milling	Montana, Texas and North Carolina, USA	1977-1980	Gravimetric	Varied by location studied
Hogue & Mallette (1949)	Rubber dusting	Vermont, USA	1943-1948	Impinger	Stated to be 'pure talc'
Dement & Shuler (1972)	Rubber dusting	Not stated (USA)	1972	Gravimetric, optical fibre counts	2-3% free silica
Fine <i>et al.</i> (1976)	Rubber dusting	Vermont, USA	1972-1974	Gravimetric	Trace of silica (<1%), <2 fibres/cm ³

Table 8. Average dust and fibre concentrations in St Lawrence County, NY, talc mining and milling operations, pre-1945-1972^a

Exposure	Dust exposure (mppcf)				Fibres ^b 1972
	Before 1945	1946-1965	1966-1969	1972	
<i>Mining</i>					
Drilling	818	5	19	7	3
Mucking	120	5	9	3	2
<i>Milling</i>					
Crushing	180	42	28	35	62
Screening	69	37	—	—	—
Milling	92	25	40	7	25
Garnering and separating	278	27	—	13	27
Pulverizing	—	28	—	—	—
Bagging	151	27	29	27	47
Box car and lorry loading	—	73	43	36	24

^aFrom Kleinfeld *et al.* (1974)^bNumber of fibres/cm³ >5 µm in length (by phase-contrast microscopy)

(2-3 fibres >5 µm/cm³), whereas exposures in mills ranged from 25-62 fibres/cm³ (Kleinfeld *et al.*, 1974). [The Working Group noted that the fibre counts represent optical counts of all fibres with a 3:1 aspect ratio and longer than 5 µm, with no further mineral identification.]

Data on time-weighted-average exposures to respirable dust and airborne fibres in the mine and mill studied by Dement *et al.* are shown in Table 9. Time-weighted average exposures to respirable dust ranged from 0.23-1.29 mg/m³ in the mine and 0.25-2.95 mg/m³ in the mill. Due to the low free silica content of this talc, exposure to respirable free silica did not exceed 0.025 mg/m³ in the mine and 0.028 mg/m³ in the mill. Airborne fibre levels measured by optical microscopy gave mean exposures in the mine and mill of 4.5 and 5.0 fibres >5 µm/cm³, respectively, with peak values as high as 29.1 fibres/cm³ in the mill. Further analyses of the airborne fibre samples by electron microscopy showed that 65% of the fibres greater than 5 µm in length were anthophyllite and 7% were tremolite. The authors concluded that the most important fibrous component of this talc deposit was anthophyllite (Dement & Zumwalde, 1979; Dement *et al.*, 1980).

Concentrations of respirable dust in mass samples from three Vermont talc mines and mills surveyed in 1975-1976 are given in Table 10. Geometric mean exposures to respirable dust ranged from 0.5 to 5.1 mg/m³ in the mines and from 0.5 to 2.9 mg/m³ in the mills; however, exposures in the mills were generally higher than those in the mines. Optical fibre counts of as much as 60 fibres/cm³ were reported. Subsequent analyses of these samples by scanning electron microscopy demonstrated rolled talc and elongated talc particles. X-ray diffraction analyses of bulk samples from these mines and mills showed that talc and magnesite were the major (20-100%) mineral components, chlorite and dolomite minor (5-20%) components, and that dolomite, calcite, quartz, biotite, ankerite, chromite,

Table 9. Respirable dust exposures and airborne fibre (longer than 5 µm) concentrations^a in a New York state talc mine and mill^b

Operation	Respirable dust				Airborne fibres				
	No. of samples	Time-weighted average ^c		Highest peak ^d (mg/m ³)	No. of samples	Time-weighted average ^c		Highest peak ^d (fibres >5 µm/cm ³)	
		Mean	Range			Mean	Median	Range	
Mine	14	0.86	0.23-1.29	1.72	54	4.5	4.4	0.8-9.8	18.2
Mill	29	0.86	0.25-2.95	4.64	168	5.0	4.3	0.2-16.0	29.1

^aBy optical microscopy^bFrom Dement and Zumwalde (1979)^cFull shift determinations^dBased on highest concentration observed in a single sample**Table 10. Respirable dust concentrations (mg/m³) in Vermont talc mines and mills^a**

Company	Area	Summer 1975		Winter 1976	
		No. of samples	Geometric mean (mg/m ³)	No. of samples	Geometric mean (mg/m ³)
A	Underground mine	18	0.6	16	0.5
	Mill (1st shift)	4	1.7	13	1.7
	Mill (2nd shift)	6	0.5	3	1.5
B	Underground mine	15	1.5	23	0.9
	Mill (1st shift)	22	1.8	42	1.8
	Mill (2nd shift)	12	2.9	16	1.9
C	Underground mine	12	0.5	19	0.7
	Walk-in mine	7	1.2		
	Walk-in mine			6	1.7
	Open-pit mine	2	5.1	—	—
	Mill # 1 (1st shift)	12	0.9	20	1.1
	Mill # 1 (3rd shift)	3	0.8	4	1.4
	Mill # 2 (1st shift)	11	1.0	8	0.5
	Mill # 2 (2nd shift)	13	0.8	3	1.1

^aFrom Boundy *et al.* (1979)

phlogopite and oligoclase were present in smaller amounts (<5%). Trace amounts of free silica were found in 15% of the samples (Boundy *et al.*, 1979). One closed mine was reported to contain tremolite microinclusions, but its fibrosity was not documented (Selevan *et al.*, 1979).

A cross-sectional study of occupational exposures in US talc mines and mills was conducted by the National Institute for Occupational Safety and Health; the results are summarized in Table 11. Bulk samples from each region were analysed by transmission electron microscopy: no fibre was found in any sample of Montana talc; fibrous tremolite and antigorite were reported in Texan talcs (0.5-3.0 µm in diameter, 4-30 µm in length); and talcs from North Carolina contained acicular cleavage fragments with particle length:diameter ratios as high as 100:1, with some <0.1 µm in diameter (Greife, 1980; Gamble *et al.*, 1982).

Table 11. Respirable dust concentrations in 275 samples from talc mines and mills located in Montana, Texas and North Carolina, USA^a

Samples	Geometric mean (mg/m ³)		
	Montana	Texas	North Carolina
From mines	0.66 (0.47-0.92) ^b	0.45 (0.18-0.71)	0.14 (0.07-0.31)
From mills	1.1 (0.85-1.41)	1.56 (0.96-2.54)	0.26 (0.13-0.51)
Bulk talc samples (% free silica)	<0.8	2.23	1.45

^aAdapted from Greife (1980) and Gamble *et al.* (1982)

^bIn parentheses, 95% frequency interval

Analysis of 362 personal samples of respirable dust collected over a full shift by the Mine Safety and Health Administration from talc mines and mills in the USA showed the median dust exposure to be 1.20 mg/m³; 90% of all exposures were to less than 2.78 mg/m³ (National Institute for Occupational Safety and Health, 1979).

Prior to adoption of technical preventive means in 1950, exposures in the talc operation in the Germanasca and Chisone Valley (Piedmont), Italy, were reported to be approximately 800 mppcf in the mines and to 25 mppcf in the mills. Exposures in both areas were reduced to less than 10 mppcf after 1965. Mineralogical analyses of these talcs demonstrated that they contained quartz, muscovite, chlorite, garnet, calcite, magnesite and small quantities of other minerals. In a few specimens, a small amount of tremolite was detected, but no other type of amphibolic asbestos or chrysotile was reported. The free silica content of powdered talc specimens was generally below the detection limits of X-ray diffraction (Rubino *et al.*, 1976). [The Working Group noted that the analytical methods were not described in detail, and the relative fibrosity of the tremolite was not documented.]

Only limited information is available about exposures in secondary industries in which talc is used or processed further. Personal air samples collected in a rubber band production plant, where housekeeping, ventilation and work practices were poor and in which talc was used as an antistick agent, had time-weighted average respirable dust concentrations of 2.5-7.8 mg/m³ (average, 4.8 mg/m³) for extruders, 5.3 and 6.1 mg/m³ for vulcanizers and 0.9 and 1.3 mg/m³ for cutters. Total dust exposures were found to range from 5.4-199 mg/m³. The talc was reported to contain 2-3% free silica. Fibre exposures, as measured by phase-contrast optical microscopy, ranged from 4.7-19.2 fibres >5 µm/cm³ (Dement & Shuler, 1972). [The Working Group noted that no electron microscopic analysis was conducted to confirm the identity of the fibres; however, most of the fibres were probably not asbestos.]

Respirable dust concentrations in two rubber manufacturing plants where Vermont talc was used as an antistick agent are shown in Table 12. Eighteen of 21 samples analysed for free silica contained less than 1% by weight. In 12 samples analysed for fibres, using optical microscopic techniques for asbestos, all concentrations were less than 2 fibres >5 µm/cm³. No electron microscopic fibre analysis was reported (Fine *et al.*, 1976). Hogue and Mallette (1949) found an average dust concentration of 15-50 mppcf talc in two rubber plants using Vermont talc. Tube machine operators had an average exposure of 20 mppcf; tube 'bookers', 35 mppcf; tube cure men, 15 mppcf; and 'line rerollers', 50 mppcf.

Table 12. Respirable dust concentrations in rubber processing plants using talc^a

Location	No. of samples	Average dust concentration (mg/m ³)
<i>Plant A</i>		
Lorry and bus inner tubes (splicer)	7	0.60
Lorry and bus inner tubes (cureman)	6	1.41
'Tuber operator'	3	0.47
'Booker'	3	0.74
Farm service inner tubes (splicer)	6	0.82
Farm service inner tubes (cureman)	2	0.91
<i>Plant B</i>		
Rubber band area	6	3.55
Gum engraving room	6	0.64
Hose extruding	4	0.51
Curing heavy duty flaps	3	1.29
'Dust room'	2	0.59

^aFrom Fine *et al.* (1976)

2.3 Analysis

Because talc is frequently contaminated with a number of other mineral phases, some known to be biologically active, an analytical protocol is often required that can distinguish among these phases.

Phase-contrast optical microscopy is a conventional technique for the identification of minerals. A microscope equipped with bright-field illumination and polarized light optics may be used to analyse talc powders (Hamer *et al.*, 1976; Boundy *et al.*, 1979; Rohl & Langer, 1979). The limitations of the technique for this purpose are discussed by Rohl *et al.* (1976).

The characteristic lines of X-ray powder diffraction pattern are 0.934, 0.468, 0.456, 0.343, 0.3115, 0.2632 and 0.2598 nm (Ross, 1984). Quantitative mineralogical analyses of bulk samples are sensitive to about 1-2% of talc (Pooley & Rowlands, 1977). The application of X-ray diffraction analysis, both continuous and step-scan modes, for quantitative determination of contaminating minerals in talc has been described, including the selection of talc and reference materials, the preparation of standard dilutions of fibres in talc to ensure sensitivity and reproducibility, the selection of characteristic X-ray reflections to be scanned, and instrumental technique. Tremolite, chrysotile and anthophyllite impurities in talc can be determined at levels as low as 0.1-2% (Rohl & Langer, 1974; Rohl *et al.*, 1976).

Morphological, structural and chemical information on single particles of talc and associated minerals can be obtained by analytical electron microscopy and selected-area electron diffraction (Rohl *et al.*, 1976).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals¹

The Working Group noted that in most of the studies of 'talc' described below, no or limited characterization of the mineralogy of the sample employed was given, and, in particular, there was a lack of information on fibre content or particle size.

(a) Oral administration

Rat: Groups of 25 male and 25 female Wistar rats, ten weeks of age, received about 50 mg/kg bw per day commercial talc [characteristics unspecified] in the diet or standard diet for life (average survival, 649 days). No significant difference in tumour incidence was found in comparison with controls (Gibel *et al.*, 1976).

A group of 16 male and 16 female Wistar-derived rats, 21-26 weeks of age, were exposed to 100 mg Italian talc (grade 00000; ready milled; mean particle size, 25 µm; containing

¹The Working Group was aware of studies in progress in mice and rats by inhalation (IARC, 1986) and in rats by subcutaneous and intraperitoneal injection (Maltoni *et al.*, 1982).

92% talc, 3% chlorite, 1% carbonate minerals and 0.5-1% quartz) per day per rat in the diet for five months and then maintained on basal diet for life (average survival, 614 days). A control group of 16 rats was fed basal diet. No difference in tumour incidence was found between the two groups (Wagner *et al.*, 1977). [The Working Group noted the limited exposure period and the advanced age of the animals at the start of exposure.]

(b) *Inhalation exposure*

Rat: A group of 24 male and 24 female Wistar-derived rats, six to eight weeks of age, was exposed by inhalation to a mean respirable dust concentration of 10.8 mg/m³ Italian talc (grade 00000; ready milled; mean particle size, 25 µm; containing 92% talc, 3% chlorite, 1% carbonate minerals and 0.5-1% quartz) for 7.5 h per day on five days a week for six (24 rats) or 12 (24 rats) months (cumulative exposures, 8200 and 16 400 mg/m³ × h, respectively). Ten days after the end of each exposure period, six rats in each group were killed; a further four rats were killed in each group one year later. Within 28 months of the start of the study, a further 12 animals in each group had died. No lung tumour was observed in rats exposed to talc for six months, while one lung adenoma occurred among those exposed for 12 months. No lung tumour was found in 24 male or 24 female controls (Wagner *et al.*, 1977). [The Working Group noted the limited number of animals allowed to survive longer than 12 months after the end of each exposure period.]

Hamster: Three groups of 50 male and 50 female Syrian golden hamsters, four weeks old, were exposed to an aerosol of talc baby powder, prepared from Vermont talc by flotation (95% w/w platy talc with trace quantities of magnesite, dolomite, chlorite and rutile), for 3, 30 or 150 min per day on five days a week for 30 days. The mean total aerosol concentration was 37.1 mg/m³, with a mean respirable fraction of 9.8 mg/m³ and a mass median aerodynamic diameter of 4.9 µm. Two further groups of hamsters, seven weeks old, were exposed to talc aerosol for 30 or 150 min per day for 300 days or until death. The mean total aerosol concentration was 27.4 mg/m³, with a mean respirable fraction of 8.1 mg/m³ and a mass median aerodynamic diameter of 6 µm. Two control groups of 25 males and 25 females were sham exposed. No primary neoplasm was found in the respiratory system of any hamster. The incidence of alveolar-cell hyperplasia was 25% in the groups exposed to aerosol for 30 or 150 min per day for 300 days, compared with 10% in the control group (Wehner *et al.*, 1977a, 1979). [The Working Group noted the inadequate duration of the study.]

(c) *Intratracheal administration*

Hamster: Groups of 24 male and 24 female Syrian golden hamsters, nine weeks old, received 18 weekly intratracheal injections of 3 mg talc (United States Pharmacopeia grade; 93.3% below 25 µm) in 0.2 ml saline, with or without 3 mg benzo[a]pyrene, or 0.2 ml saline only, or were untreated. The animals were allowed to live out their lifespan (average 50% survival, 46-55 weeks). No respiratory-tract tumour was observed in animals exposed to talc alone or in saline-treated or untreated controls. In hamsters exposed to talc with benzo[a]pyrene, 33/45 animals had benign and malignant tumours of the respiratory tract

(larynx to lung) (Stenbäck & Rowland, 1978). [The Working Group noted that no group received benzo[a]pyrene alone and that the survival in all groups was relatively short.]

(d) Subcutaneous administration

Mouse: Fifty female R3 mice, three to six months of age, were given single subcutaneous injections of 0.2 ml of a mixture of 8 g talc [unspecified] and 20 g peanut oil [dose, about 80 mg] and observed for life (average 50% survival, 596 days). No local tumour was observed (Neukomm & de Trey, 1961).

In a study reported in an abstract, female Marsh mice, three months old, received single subcutaneous injections of 20 mg USP talc and were observed for 18-21 months. No tumour developed at the injection site in 26 treated animals or in 24 saline-injected controls (Bischoff & Bryson, 1976).

(e) Intraperitoneal administration

Mouse: In a study reported in an abstract, female Marsh mice, three months old, received single intraperitoneal injections of 20 mg USP talc and were observed for 18-21 months. Intraperitoneal lymphoid tumours occurred in 5/22 treated animals and in 6/28 saline-treated controls (Bischoff & Bryson, 1976).

Forty Swiss albino mice [sex unspecified], six weeks of age, received single intraperitoneal injections of 20 mg ground commercial talc [unspecified] in saline. Before six months, 16 animals had died. In the 24 survivors allowed to live out their normal lifespan [unspecified], three peritoneal mesotheliomas were observed, compared with 3/46 in saline-treated controls (Özesmi *et al.*, 1985). [The Working Group noted the inadequate reporting of the study.]

Rat: A group of 40 female Wistar rats, eight to 12 weeks of age, received four intraperitoneal injections of 25 mg granular talc in 2 ml saline at weekly intervals. A group of 80 female rats injected with saline served as controls. The rats were observed until spontaneous death or sacrifice (average survival time after injection, 602 days). A mesothelioma was observed in 1/36 talc-exposed rats after 587 days compared with none in 72 controls (Pott *et al.*, 1974, 1976a,b).

In a study reported in an abstract, three-month-old female Evans rats received single intraperitoneal injections of 100 mg USP talc and were observed for 18-21 months. Of the treated rats, 3/27 developed tumours (one lymphosarcoma, one reticulum-cell sarcoma in the peritoneal cavity, one cystadenoma of the liver), compared with none in 26 saline-treated controls (Bischoff & Bryson, 1976).

(f) Intrapleural and intrathoracic administration

Mouse: In a study reported in an abstract, male Marsh mice, three months old, received single intrathoracic injections of 10 mg USP talc. After 18-21 months, 5/47 treated mice had tumours (two adenocarcinomas and three lymphoid tumours of the lung), compared with none of 48 saline-injected controls (Bischoff & Bryson, 1976).

Rat: In a study reported in an abstract, female Evans rats, three months old, received single intrathoracic injections of 50 mg USP talc. After 18-21 months, intrathoracic reticulum-cell sarcomas or lymphomas were observed in 7/30 talc-treated rats, in 8/32 saline-treated animals and in 7/28 untreated controls (Bischoff & Bryson, 1976).

A group of 24 male and 24 female Wistar-derived rats, eight to 14 weeks old, received single intrapleural injections of 20 mg Italian talc (grade 00000; ready milled; mean particle size, 25 µm; containing 92% talc, 3% chlorite, 1% carbonate minerals and 0.5-1% quartz). The mean survival time of the treated rats (655 days) was similar to that of 24 male and 24 female controls (691 days) injected with saline. No mesothelioma was detected in either group; one small pulmonary adenoma was found in one rat that died 25 months after injection (Wagner *et al.*, 1977).

Groups of 30-50 female Osborne-Mendel rats, 12-20 weeks old, received single intrapleural implantations of 40 mg of one of seven grades of refined commercial talc from separate sources in hardened gelatin. The rats were followed for two years, at which time survivors were killed. The incidences of pleural sarcomas were: talc 1, 1/26; talc 2, 1/30; talc 3, 1/29; talc 4, 1/29; talc 5, 0/30; talc 6, 0/30; talc 7, 0/29; compared with 3/491 in untreated controls, 17/615 in controls receiving implants of 'nonfibrous' materials described by the authors as 'noncarcinogenic' and 14/29 in rats receiving UICC crocidolite asbestos (Stanton *et al.*, 1981).

3.2 Other relevant biological data

(a) Experimental systems

Toxic effects

A review of the literature prior to 1978 on the biological effects of talc is available (Lord, 1978).

The Working Group noted that in most of the studies of 'talc' described below, no or limited characterization of the mineralogy of the sample employed was given, and, in particular, there was a lack of information on fibre content or particle size.

(i) Lethality

The LD₅₀ of talc has not been established unequivocally.

Significant mortality was observed in guinea-pigs after two or three intravenous injections of 25 mg talc in saline (Dogra *et al.*, 1977). In contrast, there was no treatment-related death in rabbits injected intravenously daily for two weeks with 100 mg talc in saline (Puro *et al.*, 1966), in rabbits receiving twice-weekly intravenous injections of 50 mg talc for ten weeks or in rats receiving twice-weekly intravenous injections of talc over a nine-week period (total dose, 100 mg) (Schepers & Durkan, 1955b). Three of 11 rats died within one day following injection of 1400 mg/kg bw talc into the lower pole of the spleen (Eger & Da Canalis, 1964).

In most of the studies described below, no acute mortality was observed in several species of animals following administration of high doses of talc by ingestion, inhalation or intratracheal, intrapleural, intraperitoneal or subcutaneous injection.

In rats fed 100 mg talc per day for 101 days, no significant depression of mean lifespan was observed (Wagner *et al.*, 1977).

Several studies of exposure to talc *via* inhalation have been reported; but, until recently (see Hanson *et al.*, 1985), the primary technical problem associated with inhalation experiments has been a lack of methods to determine accurately the amount of talc inhaled by exposed animals. The acute mortality observed in rats exposed to a 'very dense' cloud of talc (particle size, <5 µm) for 3 h per day for up to 12 days may have been due to suffocation (Policard, 1940). None of a group of rats exposed to 30-383 mg/m³ 'technical'- or 'pharmaceutical'-grade talc for 6 h per day on six days per week for up to nine months died as a specific consequence of exposure (Bethge-Iwańska, 1971). No effect was observed on the survival of hamsters exposed by inhalation to 8 mg/m³ respirable 'baby talc' for up to 150 min per day on five days per week for 300 days (Wehner *et al.*, 1977a, 1979).

A 79% mortality rate was reported in rats receiving a single intratracheal injection of 50 mg/ml talc in water. Subsequently, it was found that rats could tolerate the dose if they were given two injections of 25 mg/0.5 ml at weekly intervals (Lüchtrath & Schmidt, 1959). A 40% mortality was observed in rats injected intratracheally with 25 mg tremolitic talc/ml water (Gross *et al.*, 1970). Low mortality (2/14) was reported in chinchillas given five intratracheal injections of 40 mg talc in saline (both deaths occurred after the first injection) (Trautwein & Helmboldt, 1967).

No significant mortality was observed following intrapleural injection of 20 mg talc in saline into rats (Wagner *et al.*, 1977). Increased mortality was reported in mice six months after intraperitoneal injection of 20 mg 'commercial' talc in saline (Özesmi *et al.*, 1985), but no increased mortality was observed in rats injected intraperitoneally with 100 mg talc in saline (Pott *et al.*, 1976a). No acute toxicity was observed after a single injection of 10 mg into the bursa of rats (Hamilton *et al.*, 1984) or after suprascapular subcutaneous injection of 600 mg into mice (Carson & Kaltenbach, 1973). Transient convulsions were observed in rabbits following cisternal injection of 1 ml of a 1:9 or 1:4 suspension of talc in saline (Oppenheimer & Riester, 1953).

(ii) *Chronic toxicity*

Mild to marked arterial endothelial cell proliferation with cellular encroachment into the lumen and the occurrence of occasional foreign-body giant cells within the endothelial masses were observed after daily intravenous injections of 100 mg talc for two weeks to rabbits (Puro *et al.*, 1966). After three intravenous doses of 25 mg talc in saline to guinea-pigs, mild proliferation of the endothelial cells and moderate thickening of the intra-alveolar septa of the lungs were observed 150 days after injection (Dogra *et al.*, 1977). In contrast, no effect on the rat lung was observed after intravenous injection of talc (Schepers & Durkan, 1955b). Talc granulomas were observed in the region of Glisson's capsule following intrasplenic injection of 1400 mg/kg talc to rats (Eger & Da Canalis, 1964). After cisternal injection of talc to rabbits, no permanent neurological disorder was

seen. Microscopic examination revealed a phagocytic, histiocytic response, with some fibroblastic proliferation and dense adhesions between the membranes (Oppenheimer & Riester, 1953).

No chronic pathological effect was associated with oral administration of talc to rats (Wagner *et al.*, 1977). Intratracheal injections of talc (total dose, 150 mg) to guinea-pigs induced perivascular and peribronchiolar focal accumulations of histiocytes, fibrocytes, plasma cells and eosinophils within one month; by eight months, some fibrosis, with fibrocellular sclerosis of the pleural surface, was observed. After two years, the dominant effects were bronchiolectasia, bronchiolitis and marked fibrosis (Schepers & Durkan, 1955b).

No evidence of lung fibrosis or lymph node abnormality was observed in rats given a single intratracheal injection of 50 mg 'pure' talc in water; however, rats that received the same dose of 'calcined' (1000-1100°C) talc developed lung and lymph node fibrosis after 13 months (Lüchtrath & Schmidt, 1959). Proliferative inflammation of the smaller bronchi and bronchioles was observed in rats four days after intratracheal injection of 25 mg talc (containing tremolite; fibres, 0.1-0.2 µm in diameter) in water; within a few months, collagenous tissue had been formed (Gross *et al.*, 1970).

Chinchillas receiving a single or several intratracheal injections of 40 mg 'purified' talc in saline exhibited chronic pulmonary irritation and proliferative pneumonia, with giant-cell granulomas and adjacent metaplasia of the alveolar epithelium. The hyperplastic cells subsequently transformed into cuboid cells that formed a continuous lining of the affected alveoli and finally acquired an adenomatous appearance (Trautwein & Helmboldt, 1967).

Exposure by inhalation to a 'heavy dosing' of talc was badly tolerated by rats, causing severe dyspnoea. However, no histological change was observed within 20 days, and talc particles were trapped by alveolar macrophages (Policard, 1940). Rats exposed to dust clouds of 30-383 mg/m³ 'industrial'- or 'pharmaceutical'-grade talc for nine months developed chronic inflammatory changes, including thickening of the pulmonary arteries walls and, eventually, emphysema (Bethge-Iwańska, 1971).

In rats exposed by inhalation to 10.8 mg/m³ Italian talc (grade 00000; ready milled; mean particle size, 25 µm) for three months, minimal fibrosis was observed, the degree of which did not change during the post-exposure period. Animals exposed for one year had minimal to slight fibrosis, the degree of which had increased to moderate within one year after cessation of exposure (Wagner *et al.*, 1977). In contrast, Syrian golden hamsters exposed to 8 mg/m³ talc aerosols for up to 150 min per day on five days per week for 30 days showed no histopathological change in the lungs, heart, liver, renal tissues, stomach or uterus (Wehner *et al.*, 1977a, 1979; Wehner, 1980).

Injection of 10 mg talc (containing some asbestos fibres) into the pleural cavity of mice has been reported to produce granulomas, some of which were firmly attached to the surface of the lungs or other chest contents and, occasionally, to the lung lobes (Davis, 1972). Two years after injection of 20 mg Italian talc (see above) into the right pleural cavity of rats, granulomas at the injection site were common, and one small pulmonary adenoma was observed, but no other relevant pathology was observed in the lungs (Wagner *et al.*, 1977).

Guinea-pigs received single intraperitoneal injections of 200 mg of one of seven 'industrial'-grade talcs (up to 52% talc, up to 82% tremolite, traces of quartz). Nodules consisting of macrophages and giant cells were first observed at ten days on the ventral parietal surface and over a 15-month period became smaller. Fibroblastic proliferation was pronounced in the early phases (Schulz & Williams, 1942).

Six months after intraperitoneal injection of approximately 400 mg of a talcum powder used on surgical gloves, laparotomized albino rats exhibited typical granulomas with numerous foreign-body giant cells (Blümel *et al.*, 1962). These findings were confirmed in rats implanted with suture material dusted with talc or talc pellets, which resulted in a chronic inflammatory process with persistent granuloma formation (Sheikh *et al.*, 1984).

(iii) *Toxicity in vitro*

The concentration of talc (99% pure) required to cause 50% haemolysis of red-blood cells was 65 mg/ml, which is more than 50 fold that of chrysotile (Woodworth *et al.*, 1982).

Mouse peritoneal macrophages were exposed to seven different specimens of talc (only one of which contained amphibole fibres); all seven were found to be 'modestly' cytotoxic, as determined by the release of lactate dehydrogenase and β -glucuronidase, to a degree ten-fold less than quartz. No statistical difference was reported for the effects of the different talc samples (Davies *et al.*, 1983). The phagocytosis of talc by rabbit lung fibroblasts has been reported (Henderson *et al.*, 1975a).

A concentration of 0.1 mg/ml talc (99% pure) caused 35% release of ^{51}Cr from Syrian hamster tracheal epithelial cells labelled with sodium chromate; the concentration is two-fold that required for chrysotile (Woodworth *et al.*, 1982).

A concentration of $>50\ \mu\text{g}/\text{ml}$ Italian talc caused a 50% reduction in the colony-forming efficiency of Chinese hamster V79-4 lung cells (Chamberlain & Brown, 1978).

Effects on reproduction and prenatal toxicity

Talc was found to produce nonspecific abnormalities in chicken eggs, at an incidence similar to that induced by thalidomide and sulphadimethoxine (Carter, 1965; Yang, 1977).

No teratological effect was observed in hamsters, rats, mice or rabbits following oral administration of talc. The doses used were 1600 mg/kg bw to rats and mice on days 6-15 of gestation; 1200 mg/kg bw per day to hamsters on days 6-10 of gestation; and 900 mg/kg bw to rabbits on days 6-18 of gestation (Food and Drug Research Laboratories, 1973).

Deposition, retention and clearance

The deposition, translocation and clearance of talc in hamsters was followed by giving them a single nose-only inhalation exposure for 2 h to 40-75 mg/m³ neutron-activated talc (median diameter based on radioactivity measurements, 6.4-6.9 μm). High-grade cosmetic talc was used, consisting of 95% (w/w) platy talc mineral. Alveolar deposition was approximately 20-80 μg , representing 6-8% of the inhaled amount. The biological half-life of the talc deposited in the alveoli was seven to ten days, and alveolar clearance was reported to be essentially complete four months after exposure. [The Working Group noted that the unusually short clearance time may relate to limitations in the sensitivity of the detection

methods and the large size of the particles used.] No translocation of talc to liver, kidneys, ovaries or other parts of the body was found (Wehner *et al.*, 1977a,b).

In rats exposed to aerosols (mean respirable dust, 10.8 mg/m³) of Italian talc (see above), the mean amounts of talc retained in the lung were 2.5, 4.7 and 12.2 mg per rat following exposures for three, six and 12 months, respectively. These levels were roughly proportional to the cumulative exposures (Wagner *et al.*, 1977). In rats exposed for 6 h per day on five days per week for four weeks to 2.3, 4.3 and 17 mg/m³ respirable talc, the amounts retained in the lung at the end of exposure were 77, 187 and 806 µg talc per g lung, respectively (Hanson *et al.*, 1985).

Talc, like other foreign particles, has been found to depress the clearance of 3,4-benzo[*a*]pyrene from the lungs of hamsters (Pelfrene, 1976).

Guinea-pigs were given a single intraperitoneal injection of 200 mg of one of seven commercial talc samples (containing 3-52% talc, the rest being serpentines, carbonate, quartz and tremolite; 82% tremolite in one sample) and were examined at intervals up to 15 months. Because of differences in solubility, there was relative enrichment of the sample with talc. Talc particles were found mainly on the ventral parietal surface of the peritoneum within macrophages and giant cells (Schulz & Williams, 1942).

In studies in rats, mice, guinea-pigs and hamsters using radioactive tracer techniques, no intestinal absorption or translocation of ingested talc to the liver and kidneys was detected (Wehner *et al.*, 1977c; Phillips *et al.*, 1978). No translocation of talc into the ovaries was detected after single or multiple intravaginal applications to rabbits (Phillips *et al.*, 1978).

Mutagenicity and other short-term tests

Talc was not mutagenic to *Salmonella typhimurium* TA1530 or *his G46* or to *Saccharomyces cerevisiae* D3 *in vitro* [full details not given] or in host-mediated assays in mice (30-5000 mg/kg bw) (Litton Bionetics, 1974).

Chromosomal aberrations were not induced in human WI38 cells treated with talc at 2-200 µg/ml, and neither chromosomal aberrations nor dominant lethal mutations were induced in rats following oral administration of 30-5000 mg/kg bw talc (Litton Bionetics, 1974).

Single intraperitoneal injections of 20 mg talc plus 2 mg particulate prednisolone acetate in saline into mice induced significant numbers of multinucleated giant cells within 48 h. Neither compound alone induced this response. The multinucleate cells arose by cell fusion, and the resultant polykarions exhibited severe structural chromosomal abnormalities (bridges,acentrics and dispersed chromosomes). Prednisone in combination with talc also elicited the formation of multinucleated giant cells. Polykarions were not observed when talc was injected in combination with cortexone acetate, cortisone or testosterone isobutyrate (Dreher *et al.*, 1978).

(b) Humans

Toxic effects

The toxic effects of talc are dependent on the route, dose and properties of the talc

involved. In addition, talc commonly contains other minerals (see section 1.3), including in some instances several forms of asbestos and silica.

Talc pneumoconiosis is somewhat more prevalent and severe among people exposed to talc containing asbestiform minerals than among those exposed to talc without such impurities (Schepers & Durkan, 1955a; Kleinfeld *et al.*, 1963). The form of the pneumoconiosis varies widely, from an asymptomatic simple type (Buus-Hansen *et al.*, 1950; Vallyathan & Craighead, 1981) to disabling conglomerate pneumoconiosis (Jaques & Benirschke, 1952; Hunt, 1956; Graham & Gaensler, 1965; Fristedt *et al.*, 1968; Miller *et al.*, 1971). Mixed-dust pneumoconiosis is frequently seen, including silicosis, asbestosis and occasionally other forms (Porro *et al.*, 1942; Schepers & Durkan, 1955a; Kleinfeld *et al.*, 1963; Mark *et al.*, 1979).

Several early reports describe 'talcum powder granuloma' arising from the use of talc on surgical gloves (Antopol, 1933; Fienberg, 1937; German, 1943; Eiseman *et al.*, 1947; Diffenbaugh, 1953; Henderson *et al.*, 1975b). Subsequent cases have been reported which document a variety of surgical complications, including adhesions, pseudotumours and sinus tracts attributable to talc exposure (Lichtman *et al.*, 1946; Pruvost, 1946; Eiseman *et al.*, 1947; Saxén & Tuovinen, 1947; Enderlin *et al.*, 1959). Both skin granulomas and talc pneumoconiosis have been reported after liberal use of talc on the body (Tye *et al.*, 1966; Nam & Gracey, 1972; Wells *et al.*, 1979; Tukiainen *et al.*, 1984).

Respiratory distress syndrome, which can be fatal, has been described in children following massive accidental inhalation of talcum powder (Cless & Anger, 1954; Molnar *et al.*, 1962; Gouvéa *et al.*, 1966; Hughes & Kalmer, 1966; Lund & Feldt-Rasmussen, 1969; Niemann *et al.*, 1971; Gould & Barnardo, 1972). Acute bronchitis and bronchiolitis were found in a 22-month-old boy who died following accidental inhalation of talc (Molnar *et al.*, 1962).

A variety of pathological effects arise from intravenous use of talc containing drugs by addicts. These include micronuclear pulmonary opacities (Krainer *et al.*, 1962; Hopkins & Taylor, 1970; Szwed, 1970; Arnett *et al.*, 1976; Smith *et al.*, 1978; Waller *et al.*, 1980; Tao *et al.*, 1984), angiothrombotic pulmonary hypertension (Wendt *et al.*, 1964; Bainborough & Jericho, 1970; Zientara & Moore, 1970; Arnett *et al.*, 1976; Paré *et al.*, 1979; Waller *et al.*, 1980) and conglomerate pulmonary lesions (Sieniewicz & Nidecker, 1980; Crouch & Churg, 1983). Reduced pulmonary function has also been observed (Paré *et al.*, 1979). In addition, retinopathy, cerebral microembolization and granulomas of the liver, lymph nodes and kidneys have been reported (Lee & Sapira, 1973; Min *et al.*, 1974; Paré *et al.*, 1979; Carman, 1985).

Two studies by the US Public Health Service (Dreessen, 1933; Dreessen & Dalla Valle, 1935) of talc containing tremolite showed a high prevalence of pneumoconiosis in workers in talc mines and mills, which appeared to be related to dust concentration and duration of exposure. A variety of pneumoconiotic effects was seen, which did not appear to be related to differences in tremolite content. A series of cross-sectional studies reported from the New York State Department of Labor (Kleinfeld *et al.*, 1955; Messite *et al.*, 1959; Kleinfeld *et al.*, 1963, 1964a,b, 1973) have documented a high prevalence of talc pneumoconiosis in talc miners and millers, especially among tremolitic talc workers. The cases were associated

with pleural plaques, restrictive or obstructive breathing disorders and decreased vital capacity. The prevalence of disease was lower among those with lower cumulative dust exposure and among those processing granular rather than fibrous talc. A large, well-controlled, industry-wide study of miners and millers in four talc deposits in the USA (Gamble *et al.*, 1979a,b; Dement *et al.*, 1980; Gamble *et al.*, 1982) revealed associations between talc containing tremolite and anthophyllite and increased prevalence of bilateral pleural thickening, which was also associated with significant reductions in lung function.

A series of cross-sectional studies describing talc pneumoconiosis in workers in talc mining, milling and manufacture in Italy (Rubino *et al.*, 1963; Tronzano *et al.*, 1965) found that the prevalence was related to extent and duration of exposure and that talcs contaminated with tremolite, serpentine and quartz were associated with significant pneumoconiosis. Similarly, in studies in Egypt (El Ghawabi *et al.*, 1970; Emara *et al.*, 1984), a high prevalence of pneumoconiosis was associated with heavy exposure to talc during milling and in the cosmetics industry; obstructive and restrictive pulmonary impairment were seen among persons with pneumoconiosis.

One reasonably large, representative, well-controlled study of exposure in the rubber industry to Vermont talc, reported to have a low content of silica and fibres, showed significantly increased respiratory symptoms and impaired ventilatory function but no radiographic abnormality (Fine *et al.*, 1976).

Effects on reproduction and prenatal toxicity

No data were available to the Working Group.

Deposition, retention and clearance

Talc particles have been found at autopsy in the lungs of cases of 'talc pneumoconiosis' (Schepers & Durkan, 1955a; Seeler *et al.*, 1959; Kleinfeld *et al.*, 1963; Berner *et al.*, 1981; Vallyathan & Craighead, 1981). Talc, in the form of platy or elongated particles, has been found at autopsy in the lungs of urban residents, farmers, asbestos miners and drug addicts (Seeler *et al.*, 1959; Langer *et al.*, 1971; Pooley, 1976; Abraham & Brambilla, 1979; Gylseth *et al.*, 1984). It has been reported to be concentrated in lung scar tissue (Yao *et al.*, 1984).

Churg and Wiggs (1985) analysed by transmission electron microscopy and energy dispersive X-ray spectroscopy the total fibrous and nonfibrous mineral content of the lungs of a series of 14 male smokers with lung cancer but with no history of occupational dust exposure, and of a series of 14 control men matched by age, smoking history and general occupational class. The average concentrations of mineral fibres and nonfibrous particles were 3.8 and 2.0 times higher in the group with cancer. Kaolinite, talc, mica, feldspars and crystalline silica comprised the majority of fibrous and nonfibrous particles in both groups.

Talc particles were found in stomach tumours from Japanese men (Henderson *et al.*, 1975c), possibly due to ingestion of talc-treated rice (Merliss, 1971a,b). Talc particles, but apparently no other insoluble particle, were found in the subserosal stroma of hernia sacs, possibly due to ingestion of medications in which talc is present as a filler (Pratt *et al.*, 1985).

Talc is used as a filler in some materials that drug addicts inject, resulting in wide dissemination of talc particles to the lung (Groth *et al.*, 1972; Lamb & Roberts, 1972; Farber *et al.*, 1981; Crouch & Churg, 1983), spleen, kidney, liver, brain, heart, adrenal and thyroid (Groth *et al.*, 1972) and even the retina (AtLee, 1972). In lung, most of the talc particles are seen within the vessels of the alveolar walls, and are almost invariably associated with marked foreign body granulomas (Crouch & Churg, 1983). The talc particles found in the lung are larger after intravenous injection than after inhalation (Abraham & Brambilla, 1979).

Mutagenicity and chromosomal effects

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity to humans

(a) Case reports and case series

Individual case reports of cancer include a lung adenocarcinoma two years following talc pleurodesis (Jackson & Bennett, 1969) and a pleural mesothelioma following occupational exposure to talc (Chahinian *et al.*, 1982; Barz & Beck, 1983; Barnes & Rogers, 1984). [The Working Group noted that either these cases were associated with evidence of asbestos exposure or insufficient environmental data were available to determine whether asbestos exposure had occurred (Chahinian *et al.*, 1982).]

Four cases of mesothelioma reported to the tumour registry of the Cancer Control Bureau, New York Department of Health, USA, were associated with exposure to talc mining. Talc mines in St Lawrence County, New York, contain high levels of fibrous tremolite, the suggested etiological agent (Vianna *et al.*, 1981).

A survey of the long-term effects of talc and kaolin pleurodesis was reported by the Research Committee of the British Thoracic Association and the Medical Research Council Pneumoconiosis Unit (1979). No increase in the number of lung cancer deaths was observed, and no case of mesothelioma was reported. [The Working Group noted that there are several methodological limitations, including the fact that the duration of follow-up was less than 15 years, no data were available on smoking, and no specific information was given on the type or source of talc used.]

(b) Epidemiological studies

Kleinfeld *et al.* (1967, 1974) reported two studies on New York talc miners and millers, the results of which are substantially the same; the more complete 1974 results are reported here. Men employed in 1940, who had accumulated 15 or more years of exposure to commercial talc dust as well as those who achieved a minimum of 15 years of such exposure between 1940 and 1969, were included in this study. The cohort totalled 260 workers and was believed to represent the total work force meeting the exposure criteria. Proportionate mortality was calculated utilizing US white male mortality for the year 1955, the median year of the 108 deaths observed. Environmental exposure was reported to be predominantly to talc containing tremolite and anthophyllite (asbestiform and nonasbestiform habits),

carbonate dusts and a small amount of free silica. Further dust counts were provided for the years 1966-1969: mines had median counts ranging from 9-19 mppcf, and mills, 20-24 mppcf; dust counts and fibre counts reported for the year 1972 ranged from 3-7 mppcf and 2-3 fibres/cm³ in mines and 7-28 mppcf and 24-62 fibres/cm³ in mills. Mortality from lung and pleural cancer showed a three-fold overall increase: observed, 12%; expected, 3.7%. No significant excess was found for gastrointestinal cancers. One peritoneal mesothelioma was noted. [The Working Group noted that, as for the previously reported proportionate mortality study (Kleinfeld *et al.*, 1967), no data were available on smoking or on cumulative dose in individual workers; nor were further data given about the distribution of workers among the several mines and mills from which these records were extracted.]

A cohort mortality study was conducted of 398 white men initially employed between 1 January 1947 and 31 December 1959 in mining and milling talc in the Gouverneur Talc District of Upper New York State (St Lawrence County) (Brown *et al.*, 1979; Dement *et al.*, 1980). In addition to talc, the product contained tremolite, anthophyllite and serpentine minerals, some of which were asbestosiform. [Further details of the exposure are reported in section 2.2(b).] Vital status was ascertained as of 1975. Fifty percent of the workers had been employed less than one year and 27% for ten years or more. Statistically significant excesses in mortality were observed for all malignant neoplasms (19 observed, 10.6 expected; standardized mortality ratio [SMR], 180), for neoplasms of the respiratory system (10/3.5; SMR, 290), for bronchogenic cancer (9/3.3; SMR, 270) and for all nonmalignant respiratory disease (8/2.9; SMR, 277). Evidence of an exposure-response relationship was observed by latency for bronchogenic cancer. The authors concluded that tremolite and anthophyllite are the prime suspected etiological factors associated with the observed increase in bronchogenic cancer and nonmalignant respiratory disease in this cohort. No data on smoking were available. A possible confounding factor in this study was previous exposures at other mines in the area; however, exposures to amphibole fibre in all these regional talc operations were reported to be substantially the same.

Stille and Tabershaw (1982) conducted a cohort mortality study on the same mine and mill studied by Brown *et al.* (1979). The composition of their cohorts was somewhat different, the current study including 655 employees who had ever worked for the company between 1 January 1948 and 31 December 1977, after exclusion of 35 women office workers and 53 workers for whom birth dates or other significant data were not available. Cause-specific mortality rates were based on 113 deaths as of December 1978. The SMR for all sites of cancer was 122 (25 observed/20.5 expected); 11 cases were respiratory cancers, and ten of those were lung cancer, with SMRs of 163 and 157, respectively. The cohort was then divided according to whether an individual had been employed elsewhere before coming to work at the particular mine and mill under investigation. Those few who had worked only at the company in question were found to have very low mortality from lung cancer (two observed, 2.6 expected). [The Working Group noted a number of methodological problems, including selection bias, lack of statistical testing, small numbers of person-years of exposure, and no analysis with respect to exposure.]

Rubino *et al.* (1976) studied 1514 miners and 478 millers employed for at least one year between 1921 and 1950 in talc mines and mills in the Germanasca and Chisone valleys

(Piedmont) in Italy. The talc in those mines is described as quite pure, with only some tremolite microinclusions; no other fibrous mineral was reportedly found. [Further details of the exposure are reported in section 2.2(b).] Significant increases in specific cause of death among miners were found for silicosis (62 observed/30.9 expected) and for silico-tuberculosis (18/9.1). Significant deficits in cause-specific mortality were reported for malignant neoplasms (100/129.5), malignant neoplasms of the lung, bronchus and trachea (9/19.7) and malignant neoplasms at other sites (23/39.9). Two cases of pleural mesothelioma and a high occurrence of silicosis and silico-tuberculosis were found in the comparison group. [The Working Group noted that the method used to derive the number of expected deaths is not adequately described. It was considered that the lack of comparability between the worker and comparison groups could be the main explanation for the mortality increases and deficits observed in this study.]

Selevan *et al.* (1979) carried out a study of talc exposures in five companies (two of which ceased operations in 1952 and 1960) in three regions in Vermont, USA. Analysis of airborne dust samples and talc bulk samples revealed no asbestos, either by X-ray diffraction or analytical electron microscopy. Levels of respirable free silica were below 0.25% in nearly all ore and product samples, and free silica was only occasionally detectable in air samples. Insufficient information was available to estimate cumulative exposures, but the authors stated that past exposure levels for miners and millers far exceeded the present standard for nonfibrous talc of 20 mppcf. They considered it probable that dust exposures for millers were higher than those for miners. In one mine, which had closed by the time of the study, 'cobblestones' of highly tremolitic serpentine rock were present but were avoided or discarded as far as possible prior to milling. The cohort consisted of all white male talc workers who had been radiographed as part of annual voluntary surveys of the Vermont Health Department, who were employed in the Vermont talc industry between 1 January 1940 and 31 December 1969, and who had worked in the industry for at least one year. [Because of the voluntary nature of the survey, the cohort may not have been representative (Davis *et al.*, 1983).] There were 90 deaths among the 392 members of this cohort; vital status was not established for four. For nonmalignant respiratory disease and respiratory cancer, Vermont rates were used for comparison, because they are higher than national rates; for other causes of death, US rates were used. [The Working Group noted this unconventional analytical approach.] While some increase was noted for malignant neoplasms, and specifically for respiratory neoplasms (6 observed/3.69 expected), these were not found to be significant. [The Working Group noted that the results were not analysed by latency.] The excess of respiratory cancer occurred only among miners (5/1.15; $p < 0.05$), and the significant excess for nonmalignant respiratory disease occurred only among millers (7/1.72; $p < 0.01$). Most of those dying with nonmalignant respiratory disease had radiographic evidence of pneumoconiosis (rounded opacities). Miners were also exposed to radon daughters at mean levels ranging up to 0.12 working levels, with single peaks of 1.0 working level. [The Working Group noted that no data on smoking were available.]

In a short communication, Léophonte *et al.* (1983) reported on the mortality of talc workers in Luzenac, France. The talc in this region is said to contain no asbestos and levels of quartz varying from 0.5 to 3%. The cohort comprised those who left employment between

1 January 1945 and 31 December 1981 having worked for at least one year. Of 470 workers available for study, 256 were living, 209 had died and five were lost to follow-up; 192/204 with known occupational exposure had worked only at Luzenac. When compared with the regional population, the median age of death was not found to be influenced by dust exposure. There was no significant excess in cancer mortality in general, and, specifically, mortality from respiratory and digestive cancers was not increased. A significant increase in mortality was found for nonmalignant respiratory disease, especially for pneumoconiosis and obstructive lung disease. [The Working Group noted the unconventional definition of the cohort, that no data on smoking habits were available, and that causes of death were obtained for cases from local doctors, hospitals or families but for controls from regional or national records.]

Katsnelson and Mokronosova (1979) reported a study of mortality among workers in a talc mining and processing plant in the USSR. Very high mortality ratios were found. [The Working Group noted that the deaths observed among exposed workers included current and past workers but that the denominator comprised only currently employed persons.]

It has been suggested on the basis of ecological studies that the practice of coating rice with talc, which may be contaminated with asbestos, may play a causal role in the relatively high rate of stomach cancer in Japan (Merliss, 1971a,b; Blejer & Arlon, 1973; Matsudo *et al.*, 1974); however, this hypothesis has not been supported by case-control studies.

Cramer *et al.* (1982) reported a case-control study of ovarian cancer and talc exposure in the Boston, Massachusetts, USA, area between November 1978 and September 1981. Two-hundred-and-fifteen women with pathologically-confirmed epithelial ovarian cancers were identified and matched randomly by residence, race and age. Ninety-two (42.8%) cases regularly used talc either as a dusting powder on the perineum or on sanitary napkins compared with 61 (28.4%) controls. Adjusted for parity and menopausal status, this difference yields a relative risk of 1.9 ($p < 0.003$). Women who had regularly engaged in both practices had an adjusted relative risk of 3.3 ($p < 0.001$) compared to women with neither exposure. [The Working Group noted that while this study suggests an association between talc use and ovarian cancer, information was not available regarding the asbestos content of the talcs, levels of exposure or whether the interviews were conducted by people who were unaware of the case referent status of the person being interviewed.]

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Talc occurs in various geological settings around the world but is usually formed by alteration of ultramafic rocks or dolomites. Talc deposits may contain various other minerals, including carbonates, free silica and serpentines (including chrysotile) and amphibole minerals (asbestiform and nonasbestiform). Occupational exposures occur during mining, milling, processing and in a wide variety of secondary industries (e.g.,

ceramics, paper, rubber and paint production). Exposure of the general population occurs through use of products such as cosmetics.

4.2 Experimental data

Talc of different grades was tested for carcinogenicity in mice by subcutaneous, intraperitoneal and intrathoracic injection, in rats by oral administration, inhalation exposure and intraperitoneal, intrathoracic and intrapleural injection, and in hamsters by inhalation exposure and intratracheal instillation. The majority of these studies were inadequate. Tumour incidence was not increased following either the administration of single doses of various talcs to rats by intrapleural administration or administration of talc by four intraperitoneal injections. A single subcutaneous injection of talc in mice did not produce local tumours. No tumour was produced by administration of talc in the diet of rats. In most of the above studies, characterization of the talc was insufficient to determine whether it contained asbestos-like fibres.

No teratogenic effect was observed in rats, mice, hamsters or rabbits following oral administration of talc.

Talc was not mutagenic to *Salmonella typhimurium* or *Saccharomyces cerevisiae* in host-mediated assays. It did not induce chromosomal aberrations in cultured human cells or in rats *in vivo* or dominant lethal mutations in rats.

Overall assessment of data from short-term tests: Talc^a

	Genetic activity			Cell transformation
	DNA damage	Mutation	Chromosomal effects	
Prokaryotes	—			
Fungi/Green plants	—			
Insects				
Mammalian cells (<i>in vitro</i>)		—		
Mammals (<i>in vivo</i>)		—		
Humans (<i>in vivo</i>)				
Degree of evidence in short-term tests for genetic activity: Inadequate				Cell transformation: No data

^aThe groups into which the table is divided and the symbol ‘—’ are defined on pp. 19-20 of the Preamble; the degrees of evidence are defined on pp. 20-21.

4.3 Human data

Case reports have suggested an association between exposure to talc containing asbestos fibers and mesothelioma.

Proportionate mortality studies of miners and millers of talc containing asbestos fibers tremolite and anthophyllite showed an excess of lung cancer and one case of mesothelioma. A cohort study of workers in one company revealed significant excess mortality from lung cancer and from nonmalignant respiratory disease. Mortality from lung cancer increased with latency.

In several mortality studies, cancer risk was assessed among miners and millers of talc that was reported to contain no more than trace amounts of asbestos minerals. A cohort mortality study of talc miners and millers showed an excess of lung cancer in underground miners but not in millers; a contributory etiological role of radon daughters to the lung cancer risk in miners could not be excluded. Three other studies suffered from methodological limitations and could not be interpreted.

A case-control study suggested an approximate doubling of the risk for ovarian cancer among women after perineal use of talc.

4.4 Evaluation¹

There is *inadequate evidence* for the carcinogenicity of talc to experimental animals.

There is *inadequate evidence* for the carcinogenicity to humans of talc not containing asbestos fibers, while there is *sufficient evidence* for the carcinogenicity to humans of talc containing asbestos fibers.

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¹For definition of the italicized terms, see Preamble, pp. 18 and 22.

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ERIONITE

1. Chemical and Physical Data

1.1 Synonyms and trade names

CAS Registry No.: 66733-21-9

Chem. Abstr. Name: Erionite

1.2 Structure of typical mineral

Molecular formula: $(\text{Na}_2, \text{K}_2, \text{Ca}, \text{Mg})_{4.5} \text{Al}_9\text{Si}_{27}\text{O}_{72} \cdot 27\text{H}_2\text{O}$ (Staples & Gard, 1959; Harben & Bates, 1984)

Erionite is a zeolite. Its basic structure, like that of other zeolites, is a framework of alumino-silicate tetrahedra $(\text{Si},\text{Al})\text{O}_4$, in which each oxygen is shared between two tetrahedra. Erionite is similar in structure to and a member of the chabazite subgroup of zeolites. It has a hexagonal structure, with cell parameters of $a = 1.326 \text{ nm}$, $b = 2.308 \text{ nm}$, $c = 1.512 \text{ nm}$. The framework arrangements of linked $(\text{Si},\text{Al})\text{O}_4$ tetrahedra have been shown to form a cage-like structure which is bounded by rings consisting of four, six and eight tetrahedra. Each of these units is linked to the next by a single, shared, six-sided ring (Barrer & Kerr, 1959; Deffeyes, 1959; Staples & Gard, 1959; Sheppard & Gude, 1969; Papke, 1972; Gude & Sheppard, 1981). The structure of erionite can also be considered to be chain-like, with six tetrahedra on each edge of the unit forming part of a chain of indefinite length.

The cavities in the framework formed by the $(\text{Si},\text{Al})\text{O}_4$ tetrahedra are filled with calcium, magnesium, sodium or potassium cations together with water molecules (Papke, 1972).

1.3 Chemical and physical properties

From Roberts *et al.* (1974), unless otherwise specified

- (a) *Density:* 2.02-2.08 (Harben & Bates, 1984)
- (b) *Colour:* White
- (c) *Description:* Prismatic crystals in radiating groups; finely fibrous or wool-like; erionite is not known to occur in other than fibrous form (Albers, 1981)
- (d) *Sorption:* Sorbs up to 20 wt % water; gas absorption, ion exchange and catalytic properties are highly selective and dependent upon the molecular or ionic size of the sorbed compounds as well as upon the cation content of erionite itself.

1.4 Technical products and impurities

It is believed that erionite *per se* is not mined or marketed in any form for commercial purposes. It has been reported as a minor component in some commercial zeolites (Papke, 1972; Mondale *et al.*, 1978; Mumpton, 1983).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(a) Production

Erionite was first described and named by Eakle in 1898. The name derives from the Greek word for wool, a reference to the woolly appearance of the original specimen. No account of the occurrence of erionite was published thereafter until 1959, when several deposits in the USA were described by Deffeyes (Deffeyes, 1959; Sheppard & Gude, 1969). The first commercial synthetic zeolite was marketed in 1954 (Papke, 1972), and commercial mining of natural zeolites, including zeolite ores containing substantial amounts of erionite, began in the early 1960s (Herrick & Robinson, 1981).

There are six mineable deposits of erionite in the USA, of which only two have been mined (Mumpton, 1973). Two companies, both in the USA, were involved in the production of erionite, but both have stopped. In 1970–1972, about 120 tonnes of chabazite-erionite ore were mined in Bowie, Arizona (USA); as reported in 1979, the mining activity had been similar for several years. Open-pit mining was used. Beneficiation was sometimes employed for lower-grade zeolite ores (Mumpton, 1973; Mondale *et al.*, 1978; Herrick & Robinson, 1981; Hawkins, 1983; Mumpton, 1983).

Zeolites are mined in 16 countries: Bulgaria, China, Cuba, Czechoslovakia, the Federal Republic of Germany, Hungary, Italy, Japan, Mexico, the Republic of Korea, Romania, South Africa, Turkey, the USA, the USSR and Yugoslavia. Most of these operations are designed to mine clinoptilolite and/or mordenite, although chabazite and phillipsite are also mined (Hawkins, 1983). World production of natural zeolites has been estimated at 300 000 tonnes per year (Mumpton, 1978). Annual US production of natural zeolites was estimated to be 2500–5000 tonnes for the years 1982–1984 (Clifton, 1982, 1983, 1984).

(b) Use

Natural zeolites have many commercial uses, most of which are based on the ability of these minerals to selectively adsorb molecules from air or liquids. One such use of erionite has been documented: it was reported to be used as a noble metal-impregnated catalyst in a hydrocarbon cracking process in a US plant (Burd & Maziuk, 1972; Vaughan, 1978).

Erionite-rich blocks have been quarried in the western USA for house-building materials, but this use is thought to be very minor and not an intentional use of erionite itself (Mumpton, 1983).

It has been investigated for use to increase soil fertility (Barbarick & Pirela, 1983) and to control odours in livestock production (Miner, 1983). The extent of use for either purpose is unknown.

2.2 Occurrence

(a) Natural occurrence

Zeolite minerals are found as major constituents in numerous sedimentary volcanic tuffs, especially where these were deposited and have been altered by saline-lake water. Many hundreds of occurrences have been recorded of zeolite deposits in over 40 countries. Erionite occurs in rocks of many types (e.g., rhyolite tuff) and in a wide range of geological settings; however, it rarely occurs in pure form and is normally associated with other zeolite minerals (e.g., clinoptilolite, clinoptilolite-phillipsite, Papke, 1972; levynite, Shimazu & Mizota, 1972; chabazite, Mumpton, 1973). It is considered to have formed by the action of saline water on volcanic glass particles either by percolation or immersion. Erionite occurs as deposits of prismatic to acicular crystals several micrometers in length (Papke, 1972). When ground to powder, erionite particles resemble amphibole asbestos fibres morphologically (Deffeyes, 1959; Pooley, 1979; Mumpton, 1981).

Although named for its woolly appearance, erionite rarely occurs as this morphotype. In fact, only the initial investigation (Eakle, 1898) and the paper of Gude and Sheppard (1981) described the 'woolly' or short-fibred form, present in small deposits in Oregon and Nevada. Long-fibred erionite is found in many rock types and geological formations; most of the large deposits are found in altered lacustrine and silicic tuffs (Gude & Sheppard, 1981).

In several locations, erionite exists in deposits exceeding millions of tonnes (Deffeyes, 1959; Mumpton, 1978; Albers, 1981). Zeolite layers up to 2 m thick containing 10-100% erionite have been described in Nevada (USA) (Papke, 1972). Another major zeolite deposit containing large amounts of erionite has been reported in Japan (Shimazu & Mizota, 1972).

Small mineable deposits of erionite exist in Kenya, Mexico, New Zealand, the United Republic of Tanzania and Yugoslavia (Mumpton, 1978; Hawkins, 1983).

(b) Occupational exposure

Air samples were collected in an open-pit zeolite (containing erionite) mining operation in Bowie, Arizona, USA, in 1979. Total dust exposures for labourers ranged from 0.4-5.8 mg/m³ (eight samples); concentrations in the mining area were 0.01-13.7 mg/m³ (nine samples). Respirable dust concentrations in the mining area ranged from 0.01-1.4 mg/m³ (five samples). Airborne dust concentrations of quartz and cristobalite were below the limits of detection (0.03 mg for 100-800-litre air samples). Analyses of airborne and bulk samples by electron microscopy did not suggest substantial exposure to fibres (Herrick & Robinson, 1981).

Rock samples from a zeolite deposit in Rome, Oregon, USA, contained numerous fibres 0.02-0.5 µm in diameter and 0.5-60 µm in length. Fibrous material made up 10-30% and 8-20% of two samples taken from one erionite zone of the deposit, while the content of fibres

in a sample from another area was less than 1%. No data on occupational exposure were available, since the deposit was not being actively mined (Albers, 1981).

(c) Nonoccupational exposure

Erionite fibres have been found in soil samples from an agricultural area in Central Cappadocia, Turkey. Rock and dust samples from the villages of Tuzköy and Karain contained fibres less than $0.25\text{ }\mu\text{m}$ in diameter and more than $5\text{ }\mu\text{m}$ in length, with elemental ratios consistent with erionite (Pooley, 1979).

Baris *et al.* (1981) measured airborne fibre levels in Karain and another village in Turkey, Karlik, using transmission electron microscopy. Concentrations of fibres $>5\text{ }\mu\text{m}$ in length were below 0.01 fibres/cm^3 in the streets of both villages (20 samples), whereas concentrations in some work and recreational areas in Karain (stone cutting, fields during agricultural activity, schoolyard) ranged from $0.2\text{-}0.3\text{ fibres/cm}^3$. All indoor samples taken in Karlik contained $<0.01\text{ fibres/cm}^3$, whereas seven of the 11 indoor samples taken from Karain contained $0.03\text{-}1.38\text{ fibres/cm}^3$. Approximately 80% of respirable fibres in Karain and 20% in Karlik had chemical compositions similar to those of erionite, the rest consisting mainly of calcite.

Rohl *et al.* (1982) analysed environmental samples and lung specimens from five Cappadocian villagers and found chrysotile and tremolite fibres in addition to erionite in specimens from villages in which mesotheliomas were reported. Approximately 90% of the fibrous particles in lung tissues from patients from Karain had an elemental composition consistent with erionite.

Baris *et al.* (1987) reported the results of transmission electron microscopic analyses of more than 150 outdoor air samples collected in four Turkish villages. Levels found in streets are summarized in Table 1. Concentrations of fibres longer than $5\text{ }\mu\text{m}$ ranged from $0.001\text{-}0.029\text{ fibres/cm}^3$ in street samples; 20-85% of the fibres were identified as erionite. Concentrations as high as 0.175 fibres/cm^3 were found in a sample from a Karain schoolyard. Samples collected during sweeping of walls and floors of unoccupied houses contained up to 0.3 fibre/cm^3 erionite in Karain and up to 1 fibre/cm^3 in Sarihidir.

Table 1. Concentration and composition of fibres (longer than $5\text{ }\mu\text{m}$) in street samples from four Turkish villages^a

Village	Range (fibres/cm ³)	No. of samples	Identity
Karain	0.002-0.010	36	~80% zeolite ^b , calcium oxide, calcium sulphate
Karlik	0.002-0.006	21	~20% zeolite ^b , calcium oxide, calcium sulphate
Sarihidir	0.001-0.029	24	~60% zeolite ^b , calcite, quartz, volcanic glass, tremolite
Tuzköy	0.005-0.025	18	~85% zeolite ^b , quartz, volcanic glass, aluminium silicate

^aFrom Baris *et al.* (1987)

^bConsidered by the Working Group to be probably erionite

Rom *et al.* (1983) described the presence of fibrous erionite in samples of road dust from the Reese River area in Nevada, USA.

2.3 Analysis

Analytical electron microscopy (based on Al, Ca, Na, Mg, K and Si determinations) has been used to analyse erionite-containing dusts (Pooley, 1979; Rohl *et al.*, 1982). Selected-area electron diffraction techniques can also be used to identify erionite fibres in dust samples and lung tissue (Herrick & Robinson, 1981; Sébastien *et al.*, 1981). X-ray powder diffraction can be used to estimate the percentages of erionite and other zeolites in mineral samples (Papke, 1972); the strongest diffraction lines appear at 1.141, 0.661 and 0.4322 nm (Sheppard & Gude, 1969; Roberts *et al.*, 1974).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals¹

(a) Inhalation exposure

Rat: Groups of 20 male and 20 female Fischer 344 rats, about 57 days of age, were exposed by inhalation to concentrations of 10 mg/m³ (respirable range) Oregon erionite (56% fibres ≤ 5 µm), synthetic nonfibrous zeolite with the composition of erionite or UICC crocidolite (47.3% fibres ≤ 5 µm; 16 males and 19 females) for 7 h per day on five days per week for one year and were compared with 20 male and 20 female unexposed animals. A small number of rats were removed from the experiment at three, six, 12 and 24 months to study dust retention, leaving approximately 28 rats in each group to live out their normal lifespan, except that no rat exposed to Oregon erionite survived at 24 months. Pleural mesotheliomas were observed in 27/28 Oregon erionite-exposed rats surviving more than 12 months (mean survival, 580 days). One pulmonary adenocarcinoma and one mesothelioma were observed in 28 rats exposed to synthetic nonfibrous erionite (mean survival, 784 days), and one pulmonary squamous-cell carcinoma was found in a UICC crocidolite-exposed rat (mean survival, 917 days). No tumour of these types was observed in 28 controls (mean survival, 738 days) (Wagner *et al.*, 1985). Johnson *et al.* (1984) noted that erionite-induced pleural tumours in rats after inhalation had a similar ultrastructural appearance to mesotheliomas induced by direct inoculation of, for example, asbestos into the pleural and peritoneal cavities.

(b) Intraperitoneal administration

Mouse: Five groups of five male Swiss albino mice, four to five weeks old, received a single intraperitoneal injection of 10 or 30 mg fibrous erionite [origin unspecified] in 1 ml

¹The Working Group was aware of a study in progress and of a completed but not published study in rats by intraperitoneal injection (IARC, 1986) and of studies in progress by subcutaneous and intraperitoneal injection in rats (Maltoni *et al.*, 1982a).

saline, 10 or 30 mg mordenite [origin unspecified] or 10 mg Californian chrysotile. Six saline-injected mice served as controls. The erionite was composed of fibres 0.4-24 µm in length, with 95% shorter than 8 µm. The mordenite was a mixture of granular (0.33-5.7 µm by 0.27-1.67 µm) and fibrous (0.4-6 µm by 0.05-0.67 µm) mineral. The size of the chrysotile fibres was not reported, but the authors stated that it was 'known' that more than 90% were shorter than 1 µm. The mice were held until death (21 months). Malignant peritoneal tumours (mesotheliomas, histiocytomas or plasmacytomas) were observed in 4/5 of the group receiving 10 mg erionite and in none of the group receiving 30 mg, none of which lived longer than 11 months. Such tumours were found in 2/5 mice exposed to chrysotile asbestos but in none of those receiving mordenite or saline (Suzuki, 1982).

Groups of male BALB/c mice, five to six weeks of age, received single intraperitoneal injections of naturally occurring erionite from Colorado (erionite I; 90% <8 µm long) or Nevada (erionite II; 95% <9 µm long) or synthetic zeolite 4A (average length, 2.4 µm) in 1 ml saline and were compared with saline-treated and untreated controls. The mice were allowed to live until natural death. No peritoneal tumour was observed in animals dying before seven months. Between seven and 23 months, peritoneal tumours were seen in 21/42 receiving erionite I, 6/18 receiving 0.5 mg erionite II, 24/44 receiving 2 mg erionite II and 3/8 receiving 10 mg erionite II. Most were mesotheliomas, except that intra-abdominal plasmacytomas were observed in five mice (one receiving 0.5 mg erionite II, two receiving 2 mg erionite II and two receiving erionite I), and a pancreatic tumour occurred in one mouse receiving 2 mg erionite II. None of the animals receiving synthetic zeolite or saline or untreated controls had peritoneal tumours (Susuki & Kohyama, 1984).

Groups of 37-98 Swiss albino mice [sex unspecified], six weeks of age, received single intraperitoneal injections of 5, 10, 15, 20, 30 or 40 mg of a ground sample of rock from Karain, Turkey, 20 mg ground commercial talc [unspecified] in 1 ml saline or saline alone and were held for up to 32 months. Peritoneal mesotheliomas or malignant lymphomas were observed in mice in all groups surviving for more than six months (Table 2) (Özesmi *et al.*, 1985). [The Working Group noted the lack of information on fibre size and composition, and the occurrence of mesotheliomas in controls.]

(c) *Intrapleural administration*

Rat: In a study in progress, groups of 20 male and 20 female Sprague-Dawley rats, eight weeks old, received an intrapleural injection of 25 mg sedimentary erionite [origin and particle size unspecified] in 1 ml water or water alone. They were allowed to live until spontaneous death. After 67 weeks, 12/20 males and 9/20 females had died from pleural mesothelioma, compared with none of the 40 control rats (Maltoni *et al.*, 1982b).

Groups of 20 male and 20 female Fischer 344 rats, approximately 60 days old, received an intrapleural injection of 20 mg of either Oregon erionite, rock fibre from Karain (Turkey), nonfibrous Japanese zeolite or chrysotile asbestos in 1 ml saline or saline alone. The fibres for inoculation were collected aerodynamically from experimentally generated dust clouds. The percentages of fibres > 4 µm in length were: Oregon erionite, 40.7%; Karain rock fibre, 10.6%; [zeolite and chrysotile asbestos, not given]. The rats were observed for life. The incidences (males and females combined) of pleural mesotheliomas were 40/40

Table 2. Peritoneal mesotheliomas and malignant lymphomas in mice receiving intra-peritoneal injections of ground erionite or talc^a

Treatment	Original no. of mice	No. of mice alive at six months	No. of mice with peritoneal mesothelioma	No. of mice with malignant lymphoma
Saline	55	46	3	1
Erionite				
5 mg	69	55	6	0
10 mg	97	81	12	11
15 mg	98	73	10	7
20 mg	45	43	6	5
30 mg	45	39	3	4
40 mg	37	30	4	4
Talc	40	24	3	0

^aFrom Özesmi *et al.* (1985)

in those receiving Oregon erionite (mean survival, 390 days), 38/40 in those given Karain rock fibre (mean survival, 435 days), 2/40 in those given nonfibrous Japanese zeolite (one peritoneal; mean survival, 715 days), 19/40 in chrysotile asbestos-treated rats (mean survival, 678 days) and 1/40 in saline control rats (mean survival, 720 days) (Wagner *et al.*, 1985).

Fibrous erionite from Georgia, USSR, with a mean ratio of fibre length to diameter of 3:1 [fibre size not specified] was administered to 50 male and 50 female non-inbred white rats, weighing approximately 150 g, in three intrapleural administrations at one-month intervals of 20 mg erionite suspension in 0.5 ml saline. Controls (25 males and 25 males) received three intrapleural injections at one-month intervals of 0.5 ml saline alone. The animals were observed until death. Pleural mesotheliomas were observed in 39/40 (97.5%) treated males and 43/48 (89.6%) treated females surviving eight months or more. The first tumour was found 240 days, and the last tumour 465 days, after the beginning of the experiment. The mean survival time of rats with pleural mesotheliomas was 378 days. Pleural mesotheliomas were not observed in control rats (Pylev *et al.*, 1986).

3.2 Other relevant biological data

(a) Experimental systems

Toxic effects

After intrapleural and intraperitoneal injection of erionite in rats and mice, the main endpoint is the production of mesotheliomas, but the initial reaction is the widespread formation of granulomas in body cavities, often forming adhesions between organs. These granulomas eventually fibrose if tumour production is sufficiently delayed, and varying forms of metaplasia may be found (Maltoni *et al.*, 1982b; Suzuki, 1982).

Erionite [dose and mineralogical type unspecified] was less cytotoxic than quartz in a chemiluminescence assay employing rat peritoneal exudate cells (Korkina *et al.*, 1984). A concentration of 100 µg/ml Oregon or New Zealand erionite caused 30% release of lactic dehydrogenase from mouse peritoneal macrophages; 8 µg/ml of the Oregon sample and 12 µg/ml of the New Zealand sample reduced the colony-forming efficiency of Chinese hamster V79-4 cells by 50%; doses of 200 µg/ml caused giant-cell conversion in 25% of treated A549 lung cells with the Oregon sample and in 7.5% with the New Zealand sample. These values are comparable to those obtained with crocidolite (20% lactic dehydrogenase release, giant-cell conversion in 40% of A549 cells) (Brown *et al.*, 1980). Oregon erionite (25 µg/ml) caused a 50% decrease in the colony-forming efficiency of C3H 10T1/2 cells (Poole *et al.*, 1983).

Effects on reproduction and prenatal toxicity

No data were available to the Working Group.

Deposition, retention and clearance

An examination of the fibre content of the lungs of sheep from several Turkish villages demonstrated that animals from villages with a high mesothelioma risk had higher levels of fibrous zeolites (average, 0.13×10^6 fibres/g) than those from villages where there was no mesothelioma (average, 0.01×10^6 fibres/g). No significant difference in chrysotile concentrations was detected (Baris *et al.*, 1987).

Mutagenicity and other short-term tests

Oregon erionite induced unscheduled DNA synthesis in C3H 10T1/2 cells at concentrations of 100-200 µg/ml and in A549 human cells at concentrations of 50-200 µg/ml. At concentrations >10 µg/ml, it induced morphologically transformed foci in the C3H 10T1/2 cell transformation assay (Poole *et al.*, 1983).

(b) *Humans*

Toxic effects

Fibrosis of the lung and pleura has been observed in residents of regions in which fibrous erionite deposits occur. A 52-year-old road-construction worker from such an area in Nevada, USA, was found to have extensive pleural and parenchymal fibrosis and small pleural effusions. The patient had no history of asbestos exposure. Numerous particles and fibres chemically consistent with erionite were identified in lung tissue by electron microscopy (Casey *et al.*, 1981, 1985). Chest radiographs of 275 patients over the age of 25 years in 1968 and 1975 and over the age of 50 years in the first eight months of 1980 from a local community hospital in Nevada were also reviewed; the frequency of pleural changes (8%, including 1.8% with plaques) was not considered by the authors to be excessive for a hospital population (Rom *et al.*, 1981).

Radiological surveys were made in two Anatolian villages, Karain and Tuzköy, with high mortality from malignant mesothelial tumours and local deposits of fibrous erionite, and in two control villages, Karlik and Kizilköy, in the same area but with no fibrous

deposits. Concentrations of airborne respirable fibres were all below 0.01 fibres/cm³ in Karlik, whereas in Karain levels of up to 1.38 fibres/cm³ were detected in some locations (see section 2.2(c)). Counts of ferruginous bodies in sputum from inhabitants of the four villages confirmed the difference in exposure levels (Sébastien *et al.*, 1984). Pleural changes were slightly more prevalent in Karain than in Karlik, but the differences were not statistically significant (Baris *et al.*, 1981). In Tuzköy, pleural and parenchymal changes were observed in 10-20% of 312 subjects; no such change was found in subjects from Kizilköy (Artvinli & Baris, 1982). [The Working Group noted that the number of persons studied in Kizilköy was small (95), and it is uncertain whether the X-ray assessments were made by persons who were unaware of the case/referent status of the subject.]

Chest radiographs from Tuzköy and from Sarihidir (another village in which fibrous erionite is found) were studied further by Hillerdal and Baris (1983) and compared with films from four villages in which environmental exposure to asbestos (mainly chrysotile and tremolite), but not to erionite, occurred. In comparison to a low rate in two control villages (3/382, 0.8%), they found similar high rates of pleural calcification in the asbestos- and erionite-exposed villagers (104/446, 22.3%; and 78/549, 14.2%, respectively), but more frequent calcification of the visceral rather than parietal pleura in the erionite-exposed group.

Chest X-ray films collected in the villages of Karain and Sarihidir, where mesotheliomas are frequent, and in Karlik, where they are not, were read by a panel of three readers who were unaware of the case/referent status of the person. Interviews established that there was no difference in smoking habits among the inhabitants of the three villages. The incidence of parenchymal changes showed no clear difference between the two case villages and the control village. The percentages of pleural plaques in males were higher, but not statistically significantly so, in Karain (2.7% right side; 3.1% left side) and in Sarihidir (4.5% right side; 6.5% left side) when compared with the control village (0.9% right side; 2.5% left side). The prevalence of calcifications of the diaphragm among males was higher in Karain (4.2% right side; 2.9% left side) and in Sarihidir (6.9% right side; 6.5% left side) than in the control village (1.2% right side; 0.3% left side); the difference between Sarihidir and Karlik is statistically significant. For the other sites, the pattern of calcification was the same, but no statistically significant difference is present (Baris *et al.*, 1987).

Effects on reproduction and prenatal toxicity

No data were available to the Working Group.

Deposition, retention and clearance

The only information available on the deposition of erionite in human lung tissue comes from two cases of malignant pleural mesothelioma in central Turkey. As analysed by analytical transmission electron and optical microscopy, both cases were found to have very high concentrations of fibres (about 2×10^8 fibres/g dry lung), 93% being erionite, some of which had been transformed into ferruginous bodies similar to those formed around amphibole asbestos fibres (Sébastien *et al.*, 1981). In another study, counts were made of the numbers of ferruginous bodies in sputum from inhabitants of the Turkish villages of Karain and Tuzköy (high incidence of mesotheliomas) and from inhabitants of Karlik and Kizilköy

(control villages). In Karain and Tuzköy, 41% of the sputum samples were positive, *versus* 6% in the control villages. Up to 100 bodies/sample were found, increasing with the subject's age. Fibrous erionite appears to be rather insoluble and able to accumulate in the lung and form bodies. In that respect, its behaviour could be compared with that of amphibole asbestos (Sébastien *et al.*, 1984).

Mutagenicity and chromosomal effects

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity to humans

Baris *et al.* (1978) and Artvinli and Baris (1985) reported 11 deaths from pleural mesothelioma during 1975 and 1976 in Karain, a remote Anatolian village of 575 inhabitants; during the period 1970-1974, 24 of 55 deaths from all causes in the village were attributed to pleural mesothelioma. During 1978-1980, 27 of 67 deaths in Tuzköy, a village of 2919 inhabitants in 1977 in the same region, were ascribed to mesothelioma (12 of which were of the peritoneum) and eight to lung cancer (Artvinli & Baris, 1979, 1985).

Baris *et al.* (1987) have reported on mortality in three villages (Karain, Sarihidir, Tuzköy) in which there was exposure to erionite and in one control village (Karluk) for the years 1979-1983. Among 141 deaths in the four villages in persons aged 20 and over, 33 were ascribed to malignant mesothelioma (of which four were of the peritoneum) and 17 to lung cancer. Excess mortality from malignant mesothelioma was seen in both men and women. The mesothelioma cases were reported only in the three villages where erionite occurred, and the lung cancer deaths appeared excessive in only two; however, there were only 16 deaths from all causes in the control village.

Boman *et al.* (1982) reported three cases of pleural mesothelioma in men born in Karain who had emigrated to Sweden. A survey in 1980 of 112 persons resident in the Stockholm area and stated to be born in Karain in 1965 or earlier found radiographic evidence of pleural calcification in one subject and lung infiltration in another, but no mesothelioma.

Artvinli and Baris (1979) suggested that the presence of zeolite minerals in the soil, road dust and building stones of Tuzköy was probably the cause of the high incidence of mesothelioma and other respiratory abnormalities. This suggestion is supported by evidence of four kinds: (1) airborne respirable fibres of erionite have been found in Karain, Karluk, Sarihidir and Tuzköy but not in Kizilköy, a neighbouring village with no incidence of mesothelioma (Artvinli & Baris, 1979; Baris *et al.*, 1987); (2) erionite fibres have been found in lung tissue from two cases in Karain (Boman *et al.*, 1982) and from two cases in Tuzköy (Sébastien *et al.*, 1981); (3) ferruginous bodies with a zeolite core have been found in 14 of 34 sputum samples from residents of Karain and Tuzköy but in only two of 34 samples from two control villages, Karluk and Kizilköy (Sébastien *et al.*, 1984); (4) the age-mortality curve for cases of mesothelioma from Karain is considered to be compatible with exposure to an etiological agent in early life (Saracci *et al.*, 1982); and (5) asbestos is no more common in erionite villages than in control villages (Artvinli & Baris, 1979; Baris *et al.*, 1987).

In a case-control study of 668 fatal cases of mesothelioma in Canada (1960-1975) and in the USA (1972), 17 cases and 12 controls had lived for 20-40 years before death within 20 miles of deposits reportedly of natural zeolites in western USA. A paired analysis gave a relative risk of 1.60 after adjusting for occupational exposure to asbestos (75% confidence interval, 0.58-4.93) (McDonald & McDonald, 1980).

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Erionite occurs as a fibrous component of some zeolite deposits in various areas of the world. Erionite fibres have also been identified as a component of soil and building materials in these areas. The most important exposures to date have been nonoccupational and occur as a result of resuspension of erionite-containing dusts. Occupational exposures occur during mining, milling and processing of some zeolites as well as during agricultural work in areas in which soils are contaminated with erionite.

4.2 Experimental data

Erionite from various natural sources was tested for carcinogenicity in rats by inhalation and by intrapleural administration, and in mice by intraperitoneal injection, producing high incidences of mesotheliomas by all routes of administration.

No data were available to evaluate the reproductive or prenatal toxicity of erionite in experimental animals.

Erionite induced unscheduled DNA synthesis and morphological transformation in cultured mammalian cells.

4.3 Human data

Descriptive studies have demonstrated very high mortality from malignant mesothelioma, mainly of the pleura, in three Turkish villages where there was contamination from erionite and where exposure was from birth. Erionite fibres were identified in lung tissue samples in cases of pleural mesothelioma; ferruginous bodies were found in a much higher proportion of inhabitants in contaminated villages than in those of two control villages.

4.4 Evaluation¹

There is *sufficient evidence* for the carcinogenicity of erionite to experimental animals.

There is *sufficient evidence* for the carcinogenicity of erionite to humans.

¹For definition of the italicized terms, see Preamble, pp. 18 and 22

Overall assessment of data from short-term tests: Erionite^a

	Genetic activity			Cell transformation
	DNA damage	Mutation	Chromosomal effects	
Prokaryotes				
Fungi/Green plants				
Insects				
Mammalian cells (<i>in vitro</i>)	+			+
Mammals (<i>in vivo</i>)				
Humans (<i>in vivo</i>)				
Degree of evidence in short-term tests for genetic activity: Inadequate				Cell transformation: Positive

^aThe groups into which the table is divided and the symbol '+' are defined on pp. 19-20 of the Preamble; the degrees of evidence are defined on pp. 20-21.

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ERIONITE

237

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ERIONITE

239

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SUMMARY OF FINAL EVALUATIONS

SUMMARY OF FINAL EVALUATIONS

Compound	Degree of evidence ^a		
	Humans	Animals	Short-term tests
Silica			
crystalline	Limited	Sufficient	Inadequate
amorphous	Inadequate	Inadequate	Inadequate
Wollastonite	Inadequate	Limited	No data
Attapulgite	Inadequate	Limited	Inadequate
Sepiolite	No data	Inadequate	Inadequate
Talc	Inadequate (talc not containing asbestiform fibres) Sufficient (talc containing asbestiform fibres)	Inadequate	Inadequate
Erionite	Sufficient	Sufficient	Inadequate

^aFor definitions of the degrees of evidence, see pp. 18, 20-21 and 22 of the Preamble to this volume.

GLOSSARY

GLOSSARY

AMORPHOUS SILICA — a generic term for various SILICA forms, such as diatomite, DIATOMACEOUS EARTH, fumed silica, fused silica, vitreous silica, silica glass, silica gel, kieselguhr, colloidal silica and precipitated silica

AMORPHOUS STRUCTURE — a lack of distinct crystalline regularity in the atomic arrangement as revealed by X-ray diffraction techniques

AMPHIBOLE MINERAL — a generic term for various SILICATE MINERALS with a crystal structure composed of strips or ribbons of linked silicon-oxygen polyhedra

ASBESTOS — a term applied to six naturally occurring SILICATE MINERALS exploited commercially for their physical properties, which are in part derived from their fibrous structure. These minerals are the SERPENTINE MINERAL chrysotile and the AMPHIBOLE MINERALS crocidolite (also referred to as riebeckite asbestos), amosite (also referred to as grunerite asbestos), anthophyllite asbestos, tremolite asbestos and actinolite asbestos.

ASBESTIFORM — crystal habit of a mineral resulting in thin, hairlike fibres on a microscopic or submicroscopic level; resembling asbestos

ATTAPULGITE — a naturally occurring fibrous clay mineral (also referred to as PALYGORSKITE), with the approximate chemical formula $(\text{Mg}, \text{Al})_2\text{Si}_4\text{O}_{10}(\text{OH}) \cdot 4\text{H}_2\text{O}$ and a specific crystal structure of chain silicates

CLEAVAGE FRAGMENTATION — a proclivity of minerals, such as AMPHIBOLES, to split along definite, parallel, closely spaced planes when crushed or ground

CRISTOBALITE — see CRYSTALLINE SILICA

CRYPTOCRYSTALLINE SILICA — see MICROCRYSTALLINE SILICA

CRYSTALLINE SILICA — a generic term for several crystalline minerals composed of SILICA, such as QUARTZ, CRISTOBALITE, TRIDYMITE, coesite and stishovite

CRYSTALLINE STRUCTURE — a distinct regularity in the atomic arrangement as revealed by X-ray diffraction techniques

DIATOMACEOUS EARTH — see DIATOMITE

DIATOMITE — a siliceous deposit consisting essentially of the frustules of diatoms. The form of SILICA is biogenic OPAL but may, with geological time, devitrify to CRYSTALLINE SILICA forms such as CRISTOBALITE and TRIDYMITE.

ERIONITE — a naturally occurring fibrous ZEOLITE MINERAL with the approximate chemical formula $(\text{Na}_2, \text{K}_2, \text{Ca}, \text{Mg})_{4.5} \text{Al}_9 \text{Si}_{27} \text{O}_{72} \cdot 27 \text{H}_2\text{O}$

FIBRE — a single crystal or elongated polycrystalline aggregate which displays such properties as high aspect ratio and axial lineation

FIBRE COUNTING — for microscopic evaluation and counting of particles in dust samples, a FIBRE is commonly defined as a particle with a length greater than $5 \mu\text{m}$, a diameter of less than $3 \mu\text{m}$ and an aspect ratio greater than 3:1.

FIBRIL — the smallest unit size of a FIBROUS polycrystalline aggregate

FIBROSIS — formation of fibrous tissue as a result of injury or inflammation

FIBROUS PARTICLE — a FIBRE, fibre fragment or fibre agglomerate

MEERSCHAUM — a massive form of SEPIOLITE mineral, also referred to as β -sepiolite

MICROCRYSTALLINE SILICA — fine-grained CRYSTALLINE SILICA, which may arise by compaction and partial crystallization from AMORPHOUS SILICA of biogenic origin. These SILICA forms include such minerals as OPAL, flint, chert, chalcedony, tripoli, jasper and novaculite

OPAL — see MICROCRYSTALLINE SILICA

PALYGORSKITE — see ATTAPULGITE

PNEUMOCONIOSIS — accumulation of mineral dust in the lungs and the tissue reaction to its presence

QUARTZ — see CRYSTALLINE SILICA

SEPIOLITE — a naturally occurring fibrous clay mineral with the approximate chemical formula $\text{Mg}_2 \text{Si}_3 \text{O}_8 \cdot 2\text{H}_2\text{O}$ and a specific crystal structure of chain silicates occurring as the magnesium end-member of the paramontmorillonite-sepiolite series

SERPENTINE MINERAL — a generic term for various SILICATE MINERALS with a crystal structure composed of layered silicon-oxygen polyhedra linked by sharing all basal oxygen atoms

SILICA — CRYSTALLINE or AMORPHOUS silicon dioxide

SILICATE MINERALS — the largest group of natural minerals, with a widely varying composition but all containing silicon-oxygen tetrahedra as structural components. AMPHIBOLE, pyroxene, SERPENTINE, feldspar, mica, garnet and ZEOLITE are generic terms for some common rock-forming silicates.

SILICOSIS — PNEUMOCONIOSIS due to the inhalation of the dust of stone, sand or flint or other materials containing silicon dioxide

SOAPSTONE — a massive form of impure TALC rock

STEATITE — a massive form of high-purity TALC rock

GLOSSARY

249

TALC — a naturally occurring platy mineral with the approximate chemical formula $Mg_3Si_4O_{10}(OH)_2$ and a specific crystal structure of sheet silicates. Microscopic particles composed of talc and associated minerals may have a granular, platy, acicular or fibrous form. Different grades of talc reflect mineral ‘purity’: cosmetic- and pharmaceutical-grade talcs usually contain >90% talc mineral; industrial-grade talcs may contain substantial quantities of other minerals, such as tremolite and anthophyllite (asbestiform or nonasbestiform) and QUARTZ in varying concentrations.

TRIDYMITE — see CRYSTALLINE SILICA

WOLLASTONITE — a naturally occurring calcium metasilicate with the approximate chemical formula $CaSiO_3$ and a specific crystal structure of chain silicates

ZEOLITE MINERALS — a generic term for various crystalline aluminosilicates of alkali and alkaline earth cations, with a three-dimensional silicate structure. They are characterized by the ability to lose or gain water molecules and to exchange cations, both without major change of the crystal structure. Natural and synthetic zeolites may occur in granular or fibrous forms.

CUMULATIVE CORRIGENDA TO VOLUMES 1-41

Volume 1

p. 5

insert after line 6 Mrs I. Peterschmitt, Unit of Chemical Carcinogenesis

Lead

p. 47 3.3(b) line 2
 line 4
p. 48 reference 8

*replace 425 persons by 267 persons
replace associated with lead by related to lead
replace 213 by 313*

Auramine

p. 72 3.3(b) line 4
 lines 5-8

*after certificates add mentioning bladder tumours
replace 0.13 by 0.45
delete from The morbidity was... to the end of the paragraph*

4-Aminobiphenyl

p. 75 3.1(a) para 3 line 8

replace for life by for 2 years, 10 months or 3 years, 1 month, and replace 2 bladder papillomatoses by 3 bladder papillomas

N-Nitrosodiethylamine

p. 111 complete para 3 line 4

replace 0.04 µg/litre by 0.04 g/litre

Aflatoxins

p. 145 1.1 line 8
p. 153 line 4

*insert α after 7a and after 10a
replace µg/kg bw per day by ng/kg bw per day*

Cycasin

p. 160 line 4
p. 161 (c) line 4

*replace 13/3 by 13/13
replace Intraperitoneal by Subcutaneous*

Volume 2

Asbestos

p. 20 *after the table replace Morgan & Cralley^{MC} (1963) by Morgan & Cralley^{MC} (1973)*

p. 35 4.1 line 5 *after (less than 0.5 µm diameter and add more than*

p. 42 reference 10 *after Gilson, J.C. add Timbrell, V.*

Nickel

p. 138 complete para 2 line 3 *replace 19/21 by 19/121*

Iron-carbohydrate complexes

p. 174 4.1 para 3 line 2 *replace Iron-dextran by Iron-dextrin*

Volume 4

p. 23 *after reference 3 add Veys, C.A. (1972)
Aromatic amines — the present status of the
problem. Ann. occup. Hyg., 15, 11-15*

Aniline

p. 27 1.3(e) *replace d by n*

Magenta

p. 57 1.2(a) *in the chemical formula replace ₁₈ by ₁₉*

p. 58 (b) *in the chemical formula replace ₁₆ by ₁₇*

 (c) *in the chemical formula replace ₂₀ by ₂₁*

p. 61 (b) para 2 *replace by In the UK Carcinogenic Substances
Regulations 1967 Statutory Instrument (1967)
No. 879, magenta is listed as a controlled
substance in relation to the protection of
persons engaged in its manufacture.*

4,4'-Methylene bis(2-chloroaniline)

p. 67 lines 6-7 *delete*

4,4'-Methylenedianiline

p. 83 (b) lines 10-16 *delete from In a later study... to end of
paragraph*

CUMULATIVE CORRIGENDA TO VOLUMES 1-41

253

Volume 4 (contd)

1-Naphthylamine

p. 90 (c) last line *replace mg by ng*
p. 93 3.3(b) *delete first two lines and put reference (Case et al., 1954) in place of they in line 3*

N,N-Bis(2-chloroethyl)-2-naphthylamine (Chlornaphazine)

p. 119 1.1 *replace 49-40-31 by 494-03-1*

1,2-Dimethylhydrazine

p. 145 1.1 *replace 54-07-3 by 540-73-8*

Maleic hydrazide

p. 175 para 1 lines 3 and 8 *replace maleic anhydride by maleic hydrazide*

Bis(chloromethyl)ether

p. 231 1.1 *replace 432-88-1 by 542-88-1*

1,3-Propane sultone

p. 253 1.1
1.3(b) *replace 1633-83-6 by 1120-71-4
add at 1.4 mm after 112°C*

β -Propiolactone

p. 265 (e) line 1 *replace 0.1 mg/kg bw by 100 mg/kg bw*

Volume 5

p. 22 reference 32 *replace Abbott, D.t. by Abbott, D.C.*

DDT

p. 84 line 2 *after dichloroethane add tetrachlorodiphenylethane;*
p. 97 table *in column 3, last line, replace 69/90 by 60/90*

Volume 7

trans-2-[(Dimethylamino)methylimino]-5-[2-(5-nitro-2-furyl)vinyl]-1,3,4-oxadiazole

p. 147 1.1 *replace 259-62-77-0 by 25962-77-0*

2-(2-Formylhydrazino)-4-(5-nitro-2-furyl)thiazole

p. 157 4.1 lines 4-5 *replace renal and hepatic by renal, hepatic and*

Volume 7 (contd)

Benzene

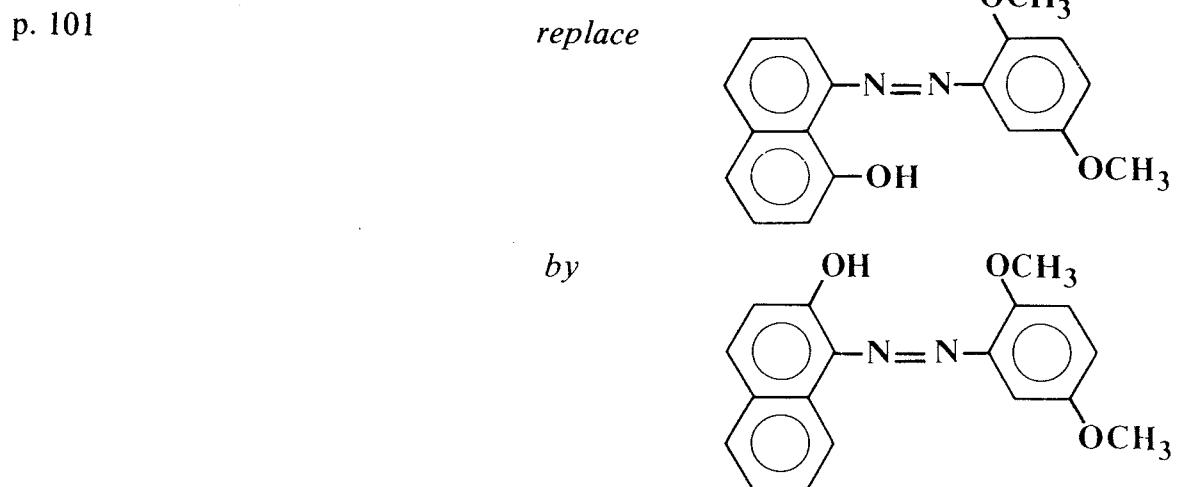
p. 215	(b) line 10	<i>replace 413 by 303 and Ten occupations by Nine occupations</i>
	line 12	<i>replace 14 controls by 13 controls</i>
	line 13	<i>replace Twenty-four by Eighteen or more</i>
	line 16	<i>replace ten occupations by nine occupations</i>

Volume 8

ortho-Aminoazotoluene

p. 68	4.	<i>Add¹ to title of section</i>
		<i>Add footnote¹ See also the section 'Animal Data in Relation to the Evaluation of Risk to Man' in the preamble to this volume, p. 15.</i>

Citrus Red no. 2



Index

p. 311	line 7	<i>delete</i>
p. 336	lines 24-25	<i>after Ponceau 3R delete see Ponceau MX 189 and see Ponceau 3R</i>

Volume 9

Mustard gas

p. 183	3.1(a) line 2	<i>replace 100 cm³ by 0.01 ml</i>
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CUMULATIVE CORRIGENDA TO VOLUMES 1-41

255

Volume 9 (contd)

Selenium

p. 245 1.1 *replace 778-24-92 by 7782-49-2*
p. 251 line 3 *replace 112 mg/kg by 1112 mg/kg*

Volume 10

p. 24 reference 32 *replace (1975) by (1976)*

Actinomycins

p. 29 1.1 line 6 *replace threo by thr*
p. 32 2.2 line 1 *replace fungi by actinomycetes*

Azaserine

p. 73 1.3 (c) *replace Refractive index: by Optical rotation:*

Native carrageenans

p. 188 line 1 *insert not between was and greater*

Parasorbic acid

p. 200 2.1 line 4 *replace (+) by (±)*

Tannic acid and tannins

p. 256 complete para 2,
line 1 *replace In addition to its natural occurrence in coffee and tea, tannic acid... by In addition to the natural occurrence of tannins in coffee and tea, tannic acid...*

Volume 11

p. 26 reference 33 *replace (1975) by (1976)*

Cadmium

p. 49 complete para 2
lines 3-5 *delete Cadmium sulphide... (Harada, 1973).*
p. 67 reference 11 *delete*

Diepoxybutane

p. 116 1.3 (c) *replace 19°C by -19°C*

Volume 11 (contd)

Epichlorohydrin

p. 133	para 5 line 3	<i>replace (15 ppm) by (5 ppm)</i>
p. 135	3.2(a) para 3 lines 7-9	<i>delete from The maximum... to end</i>
p. 138	reference 11	<i>delete</i>

Benzyl chloride

p. 222	last line	<i>replace 576-567 by 576-577</i>
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Volume 12

p. 22	reference 34	<i>replace (1975) by (1976)</i>
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Ferbam

p. 123	2.2 para 1 lines 1-3	<i>delete from For information... to end</i>
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Semicarbazide hydrochloride

p. 209	title	<i>replace SEMICARBAZIDE (HYDRO-CHLORIDE) by SEMICARBAZIDE HYDROCHLORIDE</i>
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Volume 13

Pronetalol hydrochloride

p. 229	3.1 para 3 line 1	<i>replace adequately by inadequately</i>
--------	-------------------	---

Volume 14

Asbestos

p. 33	(a) para 1 line 6	<i>replace some factories using asbestos by asbestos mills and delete ;Rickards, 1973</i>
p. 44	Table 14 line 2 para 2	<i>add 1 papillary carcinoma of lung delete</i>
p. 45	complete para 2 line 4	<i>delete ; however ... to reported</i>
p. 52	Table 19 column 1 entry 12	<i>replace Hemalite by Nemalite</i>
p. 55	entry 5	<i>delete Reeves (1976) and all data</i>

CUMULATIVE CORRIGENDA TO VOLUMES 1-41

257

Volume 14 (contd)

Asbestos (contd)

p. 67	complete para 2 line 2	<i>replace Selikoff (1976a) by Selikoff (1976b)</i>
p. 72	3.4 para 2 line 1 line 8	<i>replace has shown by reported</i> <i>add Timbrell et al., 1971; before Langer et al., 1974).</i>
p. 75	3.5 line 2	<i>replace intestinal by interstitial</i>
p. 78	entry 12	<i>replace Selikoff, 1976a by Selikoff, 1976b</i>
p. 100	reference 12	<i>delete</i>
p. 104	after reference 3	<i>add Timbrell, V., Griffiths, D.M. & Pooley, F.D. (1971) Possible biological importance of fibre diameters in South African amphiboles. Nature, 232, 55-56</i>

Volume 16

Brilliant Blue FCF diammonium and disodium salts

p. 179	para 1	<i>delete</i>
p. 182	4.1 lines 3-4	<i>delete from It also produced... to end</i>
p. 185	reference 9	<i>delete</i>

N-Phenyl-2-naphthylamine

p. 333	para 3 line 10	<i>replace Shimskaya by Shumskaya</i>
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Volume 17

N-Nitrosodiethylamine

p. 91	column 2 last line	<i>replace 4 by 3</i>
	column 3 line 7	<i>replace 62 by 67</i>
	column 4 line 7	<i>replace 4 by 62</i>

N-Nitrosodimethylamine

p. 139	(c) para 3 line 1 para 5 line 4	<i>replace mg/rat by mg/kg bw</i> <i>replace by 0.125 mg/rat at 1 day of age and</i> <i>0.125 mg/rat or 10 mg/kg bw at day 7 induced</i> <i>63%</i>
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Volume 18

p. 3 line 15 replace 29 by 37

Polychlorinated biphenyls

p. 47 footnote *delete*

Volume 19

Caprolactam and nylon 6

p. 119 3.2(a) line 1 replace LD₅₀ by LC₅₀

Styrene

p. 240 para 5 line 6 replace 350-1100 ppm by 0.35-1.2 ppm

Vinyl chloride and polymers

p. 417 para 2 line 1 *replace rats by mice*

Volume 20

Chlordane

p. 53 line 13 *replace 35/20 by 32/50*

Hexachlorocyclohexane (technical HCH and lindane)

p. 195 α -isomer, line 6 delete ; α -lindane
 β -isomer, line 5 delete ; β -lindane

p. 196 γ -isomer, lines 4-5 delete ; γ -lindane
 δ -isomer, line 5 delete ; δ -lindane
 ϵ -isomer, line 4 delete ; ϵ -lindane

p. 197 ξ -isomer, line 3 delete ; ξ -lindane
 η -isomer, line 3 delete; η -lindane

Wine

p. 283 1.1 line 10 delete Deschlorane Plus; Deschlorane Plus 515;

Volume 21

General remarks on sex hormones

p. 63 last line add a.b after (Nandi 1978)

p. 78 reference 10 add a after Nandi, S. (1978)

reference 11 add b after Nandi S (1978)

CUMULATIVE CORRIGENDA TO VOLUMES 1-41

259

Volume 21 (contd)

Diethylstilboestrol and diethylstilboestrol dipropionate

p. 227 reference 3

replace by Rüdiger, H.W., Haenisch, F., Metzler, M., Oesch, F. & Glatt, H.R. (1979) Metabolites of diethylstilbestrol which induce sister chromatid exchanges in human cultured fibroblasts. Nature, 281, 392-394

Mestranol

p. 260 para 1 line 3

replace 100 thousand-1 million by 100-1000

Oestrone and oestrone benzoate

p. 346 2.1(a) para 4 lines 3-5

delete from In 1977, ... to end

17 α -Hydroxyprogesterone caproate

p. 404 4.1 line 2

replace subcutaneous by intramuscular

Medroxyprogesterone acetate

p. 420 para 1 line 5

replace 200 thousand to 2 million by 200-2000

Norethynodrel

p. 463 para 1 line 3

replace 100 thousand to 1 million by 100-1000

lines 6-9

delete from Imports into... to end

Progesterone

p. 494 complete para 2
lines 4-5

delete from In 1977,... to end

Volume 22

Non-nutritive sweetening agents

p. 47 Iceland

replace S... + d2 by S - + m2 + d2

replace C... + d2 by C ---

p. 50 after last line

add m2 only in certain dietetic foods; maximum, 400 mg/kg

Volume 23

p. 5 List of members

add R. Althouse, University of Oxford, Clinical Medical School, Radcliffe Infirmary, Oxford, UK

Volume 23 (contd)

p. 7	Secretariat	<i>add L. Simonato, Division of Human Cancer and Field Programmes</i>
Beryllium		
p. 186	para 1 line 4	<i>replace 1051 by 1951</i>
Cumulative index		
p. 422		<i>replace Cadmium cyclamate by Calcium cyclamate</i>

Volume 24

Phenazopyridine

p. 163	after title	<i>add These compounds were considered by a previous working group, in December 1974 (IARC, 1975). Since that time, new data have become available, and these have been incorporated into the monograph and taken into account in the present evaluation.</i>
p. 171	end of page	<i>add IARC (1975) <i>IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man</i>, Vol. 8, <i>Some aromatic azo compounds</i>, Lyon, pp. 117-123</i>

Reserpine

p. 212	1.2	<i>replace CH₃COO by CH₃OOC</i>
p. 222	para 2 line 2	<i>add although there was an association with microcephaly (7 cases; relative risk, 8).</i>
p. 223	para 3 line 1	<i>replace eliminated by stimulated</i>
p. 237	reference 6	<i>add , 495 at end</i>

N-Nitrosatable drugs

p. 301	Table 2 (contd)	<i>delete and N-nitrosopiperidine</i>
	Disulfiram	

Niketamide

Volume 26

1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU)

p. 137	1.2	<i>in the structural formula replace</i>  <i>by</i> 
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CUMULATIVE CORRIGENDA TO VOLUMES 1-41

261

Volume 26 (contd)

Vinblastine sulphate

p. 349 1.2 *in the molecular formula replace H₅₉ by H₅₈*

Volume 27

para-Nitrosodiphenylamine

p. 230 3.1 line 12 *replace 12/13 by 12/31*

Volume 28

The rubber industry

p. 1 *replace February by June*

Volume 29

Benzoyl chloride

p. 59 4.3 para 2 line 4 *replace ‘benzoyl’ by ‘benzyl’*

Butyl benzyl phthalate

p. 193 1.3(f) *replace 0.782 by 0.0782*

Di(2-ethylhexyl)phthalate

p. 269 1.1 line 1 *replace 117-82-7 by 117-81-7*
p. 270 (k) *replace 0.626 by 0.0626*
p. 273 2.2 (b) para 2 line 1 *replace [0.25- 2 ppm] by [0.025-0.2 ppm]*
 (c) line 2 *replace [0.25 ppt] by [0.025 ppt] and [1.8 ppt] by [0.18 ppt]*
p. 274 line 2 *replace [0.73 ppt] by [0.073 ppt]*
p. 276 column 4 line 3 *replace [1.27-6.82 by [0.13-0.68*
p. 284 (b) para 6 line 1 *replace [0.001-0.016 mg/m³] by [0.01-0.16 mg/m³]*

Direct Black 38

p. 296 line 21 *replace Tetrodirect Black E; Tetrodirect Black EFD by Tertrodirect Black E; Tertrodirect Black EFG and insert before Tetrazo Deep Black G*

Volume 31

Ochratoxin A

p. 199 (b) line 3 *replace mycotoxin A by ochratoxin A*

Volume 32

Dibenz[*a,c*]anthracene

p. 291 complete para 3 line 3 *replace 27/28 by 27% of 28*

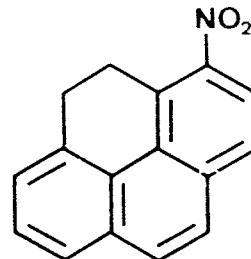
Volume 33

Mineral oils

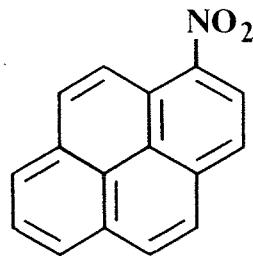
p. 94 Table 3 *replace (mg/kg) by (µg/kg)*

p. 95 Table 4 *replace (g/kg) by (µg/kg)*

p. 209 *replace*



by



Volume 36

p. 24 (iv) para 1 line 4 *replace 00 and 00 by 15-16 and 19*

CUMULATIVE CORRIGENDA TO VOLUMES 1-41

263

Volume 36 (contd)

Acetaldehyde

p.120

Replace table by

	Genetic activity			Cell transformation
	DNA damage	Mutation	Chromosomal effects	
Prokaryotes	+	+		
Fungi/Green plants		+	+	
Insects				
Mammalian cells (<i>in vitro</i>)			+	
Mammals (<i>in vivo</i>)			+	
Humans (<i>in vivo</i>)				
Degree of evidence in short-term tests for genetic activity: Sufficient				Cell transformation: No data

Ethylene oxide

p. 208 Table 8 column 1
entry 4

replace Hogstedt by Högstedt

Propylene oxide

p. 233 3.1(a) para 1
lines 10-11

should read [the inci]dences of squamous-cell carcinomas of the forestomach were 2/50 in the low-dose group and 19/50 in the high-dose group; one animal in the high-dose group had an adenocarcinoma of ...

Volume 37

Tobacco habits other than smoking

p. 73 Table 25 title

replace µg/g by µg/kg

Volume 38

Tobacco smoking

p. 9 List of members

add R.E. Kouri, B10 Corporation, 291 Whitney Avenue, New Haven, CT, USA (present address)

Volume 38 (contd)

Tobacco smoking

p. 40 Table 1

move the line Osteoporosis... <0.1 from section D and add to section C

p. 41 D lines 6-7

replace osteoporosis, with its attendant risk of fractured neck of the femur by cancer of the endometrium

Volume 39

1,3-Butadiene

p. 169 3.3 para 2 line 2

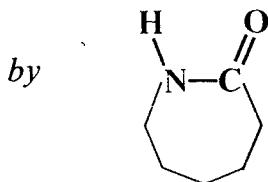
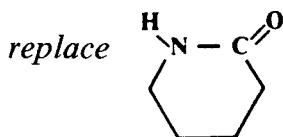
replace 1656 by 1662

p. 170 line 13

delete statistically significant and after 278. add These SMRs were not statistically significant.

Caprolactam

p. 248



Toluene diisocyanate

p. 322 reference 9

replace Vol. 13 by Vol. 23

Supplement 2

p. 18 complete para 1 line 9
complete para 2 line 8

replace exposure by effects
replace this by there

p. 364 Table 11 column 11
line 2
line 6

replace 1.245 by 1.061

p. 365 line 2
line 3

replace 4.80 by 4.62
replace 1/48, V = 4.80 by 1.49, V* = 4.62*
replace 1.48 ÷ √4.80 = 0.68 by 1.49 ÷ √4.62 = 0.69

p. 372 penultimate line

replace 192 by 191

**CUMULATIVE INDEX TO IARC MONOGRAPHS
ON THE EVALUATION OF THE CARCINOGENIC RISK
OF CHEMICALS TO HUMANS**

The volume, page and year are given. References to corrigenda are given in parentheses.

A

A- α -C (2-Amino-9 <i>H</i> -pyrido[2,3- <i>b</i>]indole)	40, 245 (1986)
Acetaldehyde	36, 101 (1985) (<i>corr.</i> 42, 263)
Acetaldehyde formylmethylhydrazone	31, 163 (1983)
Acetamide	7, 197 (1974)
Acridine orange	16, 145 (1978)
Acriflavinium chloride	13, 31 (1977)
Acrolein	19, 479 (1979) 36, 133 (1985)
Acrylamide	39, 41 (1986)
Acrylic acid	19, 47 (1979)
Acrylic fibres	19, 86 (1979)
Acrylonitrile	19, 73 (1979) <i>Suppl.</i> 4, 25 (1982)
Acrylonitrile-butadiene-styrene copolymers	19, 9 (1979)
Actinomycins	10, 29 (1976) (<i>corr.</i> 42, 255) <i>Suppl.</i> 4, 27 (1982)
Adriamycin	10, 43 (1976) <i>Suppl.</i> 4, 29 (1982)
AF-2 [2-(2-Furyl)-3-(5-nitro-2-furyl)-acrylamide]	31, 47 (1983)
Aflatoxins	1, 145 (1972) (<i>corr.</i> 42, 251)
Aflatoxin B ₁	10, 51 (1976)
Aflatoxin B ₂	<i>Suppl.</i> 4, 31 (1982)
Aflatoxin G ₁	
Aflatoxin G ₂	
Aflatoxin M ₁	
Agaritine (L-Glutamic acid-5-[2-(4-hydroxymethyl)phenylhydrazide])	31, 63 (1983)
Aldrin	5, 25 (1974) <i>Suppl.</i> 4, 35 (1982)

Allyl chloride	36, 39 (1985)
Allyl isothiocyanate	36, 55 (1985)
Allyl isovalerate	36, 69 (1985)
Aluminium production	34, 37 (1984)
Amaranth	8, 41 (1975)
5-Aminoacenaphthene	16, 243 (1978)
2-Aminoanthraquinone	27, 191 (1982)
<i>para</i> -Aminoazobenzene	8, 53 (1975)
<i>ortho</i> -Aminoazotoluene	8, 61 (1975) (corr. 42, 254)
<i>para</i> -Aminobenzoic acid	16, 249 (1978)
4-Aminobiphenyl	1, 74 (1971) (corr. 42, 251) <i>Suppl.</i> 4, 37 (1982)
1-Amino-2-methylanthraquinone	27, 199 (1982)
2-Amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole	7, 143 (1974)
4-Amino-2-nitrophenol	16, 43 (1978)
2-Amino-5-nitrothiazole	31, 71 (1983)
11-Aminoundecanoic acid	39, 239 (1986)
Amitrole	7, 31 (1974) <i>Suppl.</i> 4, 38 (1982) 41, 293 (1986)
Anaesthetics, volatile	11, 285 (1976) <i>Suppl.</i> 4, 41 (1982)
Cyclopropane	
Diethyl ether	
Enflurane	
Fluroxene	
Halothane	
Isoflurane	
Methoxyflurane	
Nitrous oxide	
Angelicin and some synthetic derivatives	40, 291 (1986)
4,4'-Dimethylangelicin	
4,5'-Dimethylangelicin	
5-Methylangelicin	
4,4',6-Trimethylangelicin	
Aniline	4, 27 (1974) (corr. 42, 252) 27, 39 (1982) <i>Suppl.</i> 4, 49 (1982)
Aniline hydrochloride	27, 40 (1982)
<i>ortho</i> -Anisidine and its hydrochloride	27, 63 (1982)
<i>para</i> -Anisidine and its hydrochloride	27, 65 (1982)
Anthanthrene	32, 95 (1983)
Anthracene	32, 105 (1983)
Anthranilic acid	16, 265 (1978)
Apholate	9, 31 (1975)
Aramite®	5, 39 (1974)

CUMULATIVE INDEX

267

Arsenic and arsenic compounds	1, 41 (1972)
Arsanilic acid	2, 48 (1973)
Arsenic pentoxide	23, 39 (1980)
Arsenic sulphide	<i>Suppl.</i> 4, 50 (1982)
Arsenic trioxide	
Arsine	
Calcium arsenate	
Dimethylarsinic acid	
Lead arsenate	
Methaneearsonic acid, disodium salt	
Methaneearsonic acid, monosodium salt	
Potassium arsenate	
Potassium arsenite	
Sodium arsenate	
Sodium arsenite	
Sodium cacodylate	
Asbestos	2, 17 (1973) (<i>corr.</i> 42, 252)
Actinolite	14 (1977) (<i>corr.</i> 42, 256-257)
Amosite	<i>Suppl.</i> 4, 52 (1982)
Anthophyllite	
Chrysotile	
Crocidolite	
Tremolite	
Attapulgite	42, 159 (1987)
Auramine	1, 69 (1972) (<i>corr.</i> 42, 251)
	<i>Suppl.</i> 4, 53 (1982) (<i>corr.</i> 33, 223)
Aurothioglucose	13, 39 (1977)
5-Azacytidine	26, 37 (1981)
Azaserine	10, 73 (1976) (<i>corr.</i> 42, 255)
Azathioprine	26, 47 (1981)
	<i>Suppl.</i> 4, 55 (1982)
Aziridine	9, 37 (1975)
2-(1-Aziridinyl)ethanol	9, 47 (1975)
Aziridyl benzoquinone	9, 51 (1975)
Azobenzene	8, 75 (1975)
B	
Benz[a]acridine	32, 123 (1983)
Benz[c]acridine	3, 241 (1973)
	32, 129 (1983)
Benzal chloride	29, 65 (1982)
	<i>Suppl.</i> 4, 84 (1982)
Benz[a]anthracene	3, 45 (1973)
	32, 135 (1983)
Benzene	7, 203 (1974) (<i>corr.</i> 42, 254)
	29, 93, 391 (1982)
	<i>Suppl.</i> 4, 56 (1982) (<i>corr.</i> 35, 249)

Benzidine and its salts	1, 80 (1972) 29, 149, 391 (1982) <i>Suppl.</i> 4, 57 (1982)
Benzo[<i>b</i>]fluoranthene	3, 69 (1973) 32, 147 (1983)
Benzo[<i>j</i>]fluoranthene	3, 82 (1973) 32, 155 (1983)
Benzo[<i>k</i>]fluoranthene	32, 163 (1983)
Benzo[<i>ghl</i>]fluoranthene	32, 171 (1983)
Benzo[<i>a</i>]fluorene	32, 177 (1983)
Benzo[<i>b</i>]fluorene	32, 183 (1983)
Benzo[<i>c</i>]fluorene	32, 189 (1983)
Benzo[<i>ghi</i>]perylene	32, 195 (1983)
Benzo[<i>c</i>]phenanthrene	32, 205 (1983)
Benzo[<i>a</i>]pyrene	3, 91 (1973) <i>Suppl.</i> 4, 227 (1982) 32, 211 (1983)
Benzo[<i>e</i>]pyrene	3, 137 (1973) 32, 225 (1983)
<i>para</i> -Benzoquinone dioxime	29, 185 (1982)
Benzotrichloride	29, 73 (1982) <i>Suppl.</i> 4, 84 (1982)
Benzoyl chloride	29, 83 (1982) (<i>corr.</i> 42, 261) <i>Suppl.</i> 4, 84 (1982)
Benzoyl peroxide	36, 267 (1985)
Benzyl acetate	40, 109 (1986)
Benzyl chloride	11, 217 (1976) (<i>corr.</i> 42, 256) 29, 49 (1982) (<i>corr.</i> 42, 261) <i>Suppl.</i> 4, 84 (1982)
Benzyl violet 4B	16, 153 (1978)
Beryllium and beryllium compounds	1, 17 (1972) 23, 143 (1980) (<i>corr.</i> 42, 260) <i>Suppl.</i> 4, 60 (1982)
Bertrandite	
Beryllium acetate	
Beryllium acetate, basic	
Beryllium-aluminium alloy	
Beryllium carbonate	
Beryllium chloride	
Beryllium-copper alloy	
Beryllium-copper-cobalt alloy	
Beryllium fluoride	
Beryllium hydroxide	
Beryllium-nickel alloy	
Beryllium oxide	
Beryllium phosphate	
Beryllium silicate	
Beryllium sulphate and its tetrahydrate	
Beryl ore	
Zinc beryllium silicate	

CUMULATIVE INDEX

269

Betel-quid and areca-nut chewing 37, 141 (1985)
Bis(1-aziridinyl)morpholinophosphine sulphide 9, 55 (1975)
Bis(2-chloroethyl)ether 9, 117 (1975)
N,N-Bis(2-chloroethyl)-2-naphthylamine 4, 119 (1974) (*corr.* 42, 253)
(Chlornaphazine) *Suppl.* 4, 62 (1982)
Bischloroethyl nitrosourea (BCNU) 26, 79 (1981)
Suppl. 4, 63 (1982)
1,2-Bis(chloromethoxy)ethane 15, 31 (1977)
1,4-Bis(chloromethoxymethyl)benzene 15, 37 (1977)
Bis(chloromethyl)ether 4, 231 (1974) (*corr.* 42, 253)
Suppl. 4, 64 (1982)
Bis(2-chloro-1-methylethyl)ether 41, 149 (1986)
Bitumens 35, 39 (1985)
Bleomycins 26, 97 (1981)
Suppl. 4, 66 (1982)
Blue VRS 16, 163 (1978)
Boot and shoe manufacture and repair 25, 249 (1981)
Suppl. 4, 138 (1982)
Bracken fern 40, 47 (1986)
Brilliant Blue FCF diammonium and disodium salts 16, 171 (1978) (*corr.* 42, 257)
1,3-Butadiene 39, 155 (1986) (*corr.* 42, 264)
1,4-Butanediol dimethanesulphonate (Myleran) 4, 247 (1974)
Suppl. 4, 68 (1982)
n-Butyl acrylate 39, 67 (1986)
Butylated hydroxyanisole (BHA) 40, 123 (1986)
Butylated hydroxytoluene (BHT) 40, 161 (1986)
Butyl benzyl phthalate 29, 193 (1982) (*corr.* 42, 261)
 β -Butyrolactone 11, 225 (1976)
 γ -Butyrolactone 11, 231 (1976)

C

Cadmium and cadmium compounds 2, 74 (1973)
Cadmium acetate 11, 39 (1976) (*corr.* 42, 255)
Cadmium chloride *Suppl.* 4, 71 (1982)
Cadmium oxide
Cadmium sulphate
Cadmium sulphide
Calcium cyclamate 22, 58 (1980)
Suppl. 4, 97 (1982)
Calcium saccharin 22, 120 (1980)
Suppl. 4, 225 (1982)
Cantharidin 10, 79 (1976)
Caprolactam 19, 115 (1979) (*corr.* 42, 258)
39, 247 (1986) (*corr.* 42, 264)
Captan 30, 295 (1983)

Carbaryl	12, 37 (1976)
Carbazole	32, 239 (1983)
3-Carbethoxypsoralen	40, 317 (1986)
Carbon blacks	3, 22 (1973) 33, 35 (1984)
Carbon tetrachloride	1, 53 (1972) 20, 371 (1979) <i>Suppl.</i> 4, 74 (1982)
Carmoisine	8, 83 (1975)
Carpentry and joinery	25, 139 (1981) <i>Suppl.</i> 4, 139 (1982)
Carrageenan	10, 181 (1976) (<i>corr.</i> 42, 255) 31, 79 (1983)
Catechol	15, 155 (1977)
Chlorambucil	9, 125 (1975) 26, 115 (1981) <i>Suppl.</i> 4, 77 (1982)
Chloramphenicol	10, 85 (1976) <i>Suppl.</i> 4, 79 (1982)
Chlordane	20, 45 (1979) (<i>corr.</i> 42, 258) <i>Suppl.</i> 4, 80 (1982)
Chlordecone (Kepone)	20, 67 (1979)
Chlordimeform	30, 61 (1983)
Chlorinated dibenzodioxins	15, 41 (1977) <i>Suppl.</i> 4, 211, 238 (1982)
Chlorinated toluenes (production of)	<i>Suppl.</i> 4, 84 (1982)
Chlormadinone acetate	6, 149 (1974) 21, 365 (1979) <i>Suppl.</i> 4, 192 (1982)
Chlorobenzilate	5, 75 (1974) 30, 73 (1983)
Chlorodifluoromethane	41, 237 (1986)
1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU)	26, 173 (1981) (<i>corr.</i> 42, 260) <i>Suppl.</i> 4, 83 (1982)
Chlorofluoromethane	41, 229 (1986)
Chloroform	1, 61 (1972) 20, 401 (1979) <i>Suppl.</i> 4, 87 (1982)
Chloromethyl methyl ether	4, 239 (1974) <i>Suppl.</i> 4, 64 (1982)
Chlorophenols (occupational exposures to)	<i>Suppl.</i> 4, 88 (1982)
Chlorophenoxy herbicides (occupational exposures to) (<i>see also</i> Phenoxyacetic acid herbicides, occupational exposure to)	41, 319 (1986) 41, 357 (1986)

CUMULATIVE INDEX

271

4-Chloro- <i>ortho</i> -phenylenediamine	27, 81 (1982)
4-Chloro- <i>meta</i> -phenylenediamine	27, 82 (1982)
Chloroprene	19, 131 (1979) <i>Suppl.</i> 4, 89 (1982)
Chloroprophan	12, 55 (1976)
Chloroquine	13, 47 (1977)
Chlorothalonil	30, 319 (1983)
<i>para</i> -Chloro- <i>ortho</i> -toluidine and its hydrochloride	16, 277 (1978) 30, 65 (1983)
Chlorotrianisene	21, 139 (1979)
2-Chloro-1,1,1-trifluoroethane	41, 253 (1986)
Cholesterol	10, 99 (1976) 31, 95 (1983)
Chromium and chromium compounds	2, 100 (1973) 23, 205 (1980) <i>Suppl.</i> 4, 91 (1982)
Barium chromate	
Basic chromic sulphate	
Calcium chromate	
Chromic acetate	
Chromic chloride	
Chromic oxide	
Chromic phosphate	
Chromite ore	
Chromium carbonyl	
Chromium potassium sulphate	
Chromium sulphate	
Chromium trioxide	
Cobalt-chromium alloy	
Ferrochromium	
Lead chromate	
Lead chromate oxide	
Potassium chromate	
Potassium dichromate	
Sodium chromate	
Sodium dichromate	
Strontium chromate	
Zinc chromate	
Zinc chromate hydroxide	
Zinc potassium chromate	
Zinc yellow	
Chrysene	3, 159 (1973) 32, 247 (1983)
Chrysoidine	8, 91 (1975)
C.I. Disperse Yellow 3	8, 97 (1975)
Cinnamyl anthranilate	16, 287 (1978) 31, 133 (1983)
Cisplatin	26, 151 (1981) <i>Suppl.</i> 4, 93 (1982)

Citrinin	40, 67 (1986)
Citrus Red No. 2	8, 101 (1975) (<i>corr.</i> 42, 254)
Clofibrate	24, 39 (1980) <i>Suppl.</i> 4, 95 (1982)
Clomiphene and its citrate	21, 551 (1979) <i>Suppl.</i> 4, 96 (1982)
Coal gasification	34, 65 (1984)
Coal-tar pitches (<i>see</i> Coal-tars)	
Coal-tars	35, 83 (1985)
Coke production	34, 101 (1984)
Conjugated oestrogens	21, 147 (1979) <i>Suppl.</i> 4, 179 (1982)
Copper 8-hydroxyquinoline	15, 103 (1977)
Coronene	32, 263 (1983)
Coumarin	10, 113 (1976)
Creosotes (<i>see</i> Coal-tars)	
<i>meta</i> -Cresidine	27, 91 (1982)
<i>para</i> -Cresidine	27, 92 (1982)
Cycasin	1, 157 (1972) (<i>corr.</i> 42, 251) 10, 121 (1976)
Cyclamic acid	22, 55 (1980) <i>Suppl.</i> 4, 97 (1982)
Cyclochlorotine	10, 139 (1976)
Cyclohexylamine	22, 59 (1980) <i>Suppl.</i> 4, 97 (1982)
Cyclopenta[cd]pyrene	32, 269 (1983)
Cyclophosphamide	9, 135 (1975) 26, 165 (1981) <i>Suppl.</i> 4, 99 (1982)
D	
2,4-D and esters (<i>see also</i> Chlorophenoxy herbicides, occupational exposures to)	15, 111 (1977) <i>Suppl.</i> 4, 101, 211 (1982)
Dacarbazine	26, 203 (1981) <i>Suppl.</i> 4, 103 (1982)
D & C Red No. 9	8, 107 (1975)
Dapsone	24, 59 (1980) <i>Suppl.</i> 4, 104 (1982)
Daunomycin	10, 145 (1976)
DDT and associated substances	5, 83 (1974) (<i>corr.</i> 42, 253) <i>Suppl.</i> 4, 105 (1982)
DDD (TDE)	
DDE	
Diacetylaminooazotoluene	8, 113 (1975)
<i>N,N'</i> -Diacetylbenzidine	16, 293 (1978)
Diallate	12, 69 (1976) 30, 235 (1983)
2,4-Diaminoanisole and its sulphate	16, 51 (1978) 27, 103 (1982)

CUMULATIVE INDEX

273

4,4'-Diaminodiphenyl ether	16, 301 (1978) 29, 203 (1982)
1,2-Diamino-4-nitrobenzene	16, 63 (1978)
1,4-Diamino-2-nitrobenzene	16, 73 (1978)
2,4-Diaminotoluene (<i>see also</i> Toluene diisocyanate)	16, 83 (1978)
2,5-Diaminotoluene and its sulphate	16, 97 (1978)
Diazepam	13, 57 (1977)
Diazomethane	7, 223 (1974)
Dibenz[<i>a,h</i>]acridine	3, 247 (1973) 32, 277 (1983) 3, 254 (1973) 32, 283 (1983)
Dibenz[<i>a,f</i>]acridine	32, 289 (1983) (<i>corr.</i> 42, 262) 3, 178 (1973) 32, 299 (1983)
Dibenz[<i>a,c</i>]anthracene	32, 309 (1983)
Dibenz[<i>a,h</i>]anthracene	3, 260 (1973) 32, 315 (1983)
Dibenz[<i>a,f</i>]anthracene	32, 321 (1983)
7 <i>H</i> -Dibenzo[<i>c,g</i>]carbazole	3, 197 (1973)
Dibenzo[<i>a,e</i>]fluoranthene	3, 201 (1973) 32, 327 (1983)
Dibenzo[<i>h,rst</i>]pentaphene	32, 331 (1983)
Dibenzo[<i>a,e</i>]pyrene	3, 207 (1973) 32, 331 (1983)
Dibenzo[<i>a,h</i>]pyrene	3, 215 (1973) 32, 337 (1983)
Dibenzo[<i>a,i</i>]pyrene	3, 224 (1973) 32, 343 (1983)
Dibenzo[<i>a,l</i>]pyrene	15, 139 (1977) 20, 83 (1979) 39, 369 (1986)
1,2-Dibromo-3-chloropropane	7, 231 (1974) 29, 213 (1982) <i>Suppl.</i> 4, 108 (1982)
Dichloroacetylene	7, 231 (1974)
<i>ortho</i> -Dichlorobenzene	29, 215 (1982) <i>Suppl.</i> 4, 108 (1982)
<i>para</i> -Dichlorobenzene	4, 49 (1974) 29, 239 (1982) <i>Suppl.</i> 4, 110 (1982)
3,3'-Dichlorobenzidine and its dihydrochloride	15, 149 (1977) 16, 309 (1978) 20, 429 (1979) 20, 449 (1979) <i>Suppl.</i> 4, 111 (1982)
<i>trans</i> -1,4-Dichlorobutene	41, 43 (1986)
3,3'-Dichloro-4,4'-diaminodiphenyl ether	
1,2-Dichloroethane	
Dichloromethane	

2,6-Dichloro- <i>para</i> -phenylenediamine	39, 325 (1986)
1,2-Dichloropropane	41, 131 (1986)
1,3-Dichloropropene	41, 113 (1986)
Dichlorvos	20, 97 (1979)
Dicofol	30, 87 (1983)
Dicyclohexylamine	22, 60 (1980)
Dieldrin	5, 125 (1974) <i>Suppl.</i> 4, 112 (1982)
Dienoestrol	21, 161 (1979) <i>Suppl.</i> 4, 183 (1982)
Diepoxybutane	11, 115 (1976) (<i>corr.</i> 42, 255)
Di(2-ethylhexyl)adipate	29, 257 (1982)
Di(2-ethylhexyl)phthalate	29, 269 (1982) (<i>corr.</i> 42, 261)
1,2-Diethylhydrazine	4, 153 (1974)
Diethylstilboestrol	6, 55 (1974) 21, 172 (1979) (<i>corr.</i> 42, 259) <i>Suppl.</i> 4, 184 (1982)
Diethylstilboestrol dipropionate	21, 175 (1979)
Diethyl sulphate	4, 277 (1974) <i>Suppl.</i> 4, 115 (1982)
Diglycidyl resorcinol ether	11, 125 (1976)
Dihydrosafrole	36, 181 (1985) 1, 170 (1972) 10, 233 (1976)
Dihydroxybenzenes	15, 155 (1977)
Dihydroxymethylfuratrizine	24, 77 (1980)
Dimethisterone	6, 167 (1974) 21, 377 (1979) <i>Suppl.</i> 4, 193 (1982)
Dimethoxane	15, 177 (1977)
3,3'-Dimethoxybenzidine (<i>ortho</i> -Dianisidine)	4, 41 (1974) <i>Suppl.</i> 4, 116 (1982)
3,3'-Dimethoxybenzidine-4,4'-diisocyanate	39, 279 (1986)
<i>para</i> -Dimethylaminoazobenzene	8, 125 (1975)
<i>para</i> -Dimethylaminoazobenzenediazosodium sulphonate	8, 147 (1975)
<i>trans</i> -2-[(Dimethylamino)methylimino]-5-[2-(5-nitro-2-furyl)-vinyl]-1,3,4-oxadiazole	7, 147 (1974) (<i>corr.</i> 42, 253)
3,3'-Dimethylbenzidine (<i>ortho</i> -Tolidine)	1, 87 (1972)
Dimethylcarbamoyl chloride	12, 77 (1976) <i>Suppl.</i> 4, 118 (1982)
1,1-Dimethylhydrazine	4, 137 (1974)
1,2-Dimethylhydrazine	4, 145 (1974) (<i>corr.</i> 42, 253)
1,4-Dimethylphenanthrene	32, 349 (1983)
Dimethyl sulphate	4, 271 (1974) <i>Suppl.</i> 4, 119 (1982)
1,8-Dinitropyrene	33, 171 (1984)
Dinitrosopentamethylenetetramine	11, 241 (1976)

CUMULATIVE INDEX

275

1,4-Dioxane	11, 247 (1976) <i>Suppl.</i> 4, 121 (1982)
2,4'-Diphenyldiamine	16, 313 (1978)
Direct Black 38	29, 295 (1982) (<i>corr.</i> 42, 261) <i>Suppl.</i> 4, 59 (1982)
Direct Blue 6	29, 311 (1982) <i>Suppl.</i> 4, 59 (1982)
Direct Brown 95	29, 321 (1982) <i>Suppl.</i> 4, 59 (1982)
Disulfiram	12, 85 (1976)
Dithranol	13, 75 (1977)
Dulcin	12, 97 (1976)
E	
Endrin	5, 157 (1974)
Eosin and its disodium salt	15, 183 (1977)
Epichlorohydrin	11, 131 (1976) (<i>corr.</i> 42, 256) <i>Suppl.</i> 4, 122 (1982) (<i>corr.</i> 33, 223)
1-Epoxyethyl-3,4-epoxycyclohexane	11, 141 (1976)
3,4-Epoxy-6-methylcyclohexylmethyl-3,4-epoxy-6-methylcyclohexane carboxylate	11, 147 (1976)
cis-9,10-Epoxystearic acid	11, 153 (1976)
Erionite	42, 225 (1987)
Ethinyloestradiol	6, 77 (1974) 21, 233 (1979) <i>Suppl.</i> 4, 186 (1982)
Ethionamide	13, 83 (1977)
Ethyl acrylate	19, 57 (1979) 39, 81 (1986)
Ethylene	19, 157 (1979)
Ethylene dibromide	15, 195 (1977) <i>Suppl.</i> 4, 124 (1982)
Ethylene oxide	11, 157 (1976) <i>Suppl.</i> 4, 126 (1982)
Ethylene sulphide	36, 189 (1985) (<i>corr.</i> 42, 263)
Ethylene thiourea	11, 257 (1976) 7, 45 (1974) <i>Suppl.</i> 4, 128 (1982)
Ethyl methanesulphonate	7, 245 (1974)
Ethyl selenac	12, 107 (1976)
Ethyl tellurac	12, 115 (1976)
Ethynodiol diacetate	6, 173 (1974) 21, 387 (1979) <i>Suppl.</i> 4, 194 (1982)
Eugenol	36, 75 (1985)
Evans blue	8, 151 (1975)

F

Fast Green FCF	16, 187 (1978)
Ferbam	12, 121 (1976) (<i>corr.</i> 42, 256)
Fluometuron	30, 245 (1983)
Fluoranthene	32, 355 (1983)
Fluorene	32, 365 (1983)
Fluorides (inorganic, used in drinking-water and dental preparations)	27, 237 (1982)
Fluorspar	
Fluosilicic acid	
Sodium fluoride	
Sodium monofluorophosphate	
Sodium silicofluoride	
Stannous fluoride	
5-Fluorouracil	26, 217 (1981) <i>Suppl.</i> 4, 130 (1982)
Formaldehyde	29, 345 (1982) <i>Suppl.</i> 4, 131 (1982)
2-(2-Formylhydrazino)-4-(5-nitro-2-furyl)thiazole	7, 151 (1974) (<i>corr.</i> 42, 253)
Furazolidone	31, 141 (1983)
The furniture and cabinet-making industry	25, 99 (1981) <i>Suppl.</i> 4, 140 (1982)
Fusarenon-X	11, 169 (1976) 31, 153 (1983)

G

Glu-P-1 (2-Amino-6-methylidopyrido[1,2- <i>a</i> :3', 2'- <i>d</i>]imidazole	40, 223 (1986)
Glu-P-2 (2-Aminodipyrido[1,2- <i>a</i> :3',2'- <i>d</i>]-imidazole	40, 235 (1986)
Glycidaldehyde	11, 175 (1976)
Glycidyl oleate	11, 183 (1976)
Glycidyl stearate	11, 187 (1976)
Griseofulvin	10, 153 (1976)
Guinea Green B	16, 199 (1978)
Gyromitrin	31, 163 (1983)

H

Haematite	1, 29 (1972) <i>Suppl.</i> 4, 254 (1982)
Hair dyes, epidemiology of	16, 29 (1978) 27, 307 (1982)

IARC MONOGRAPHS VOLUME 42

277

Heptachlor and its epoxide	5, 173 (1974) 20, 129 (1979) <i>Suppl.</i> 4, 80 (1982)
Hexachlorobenzene	20, 155 (1979)
Hexachlorobutadiene	20, 179 (1979)
Hexachlorocyclohexane (α -, β -, δ -, ϵ -,technical HCH and lindane)	5, 47 (1974) 20, 195 (1979) (<i>corr.</i> 42, 258) <i>Suppl.</i> 4, 133 (1982)
Hexachloroethane	20, 467 (1979)
Hexachlorophene	20, 241 (1979)
Hexamethylphosphoramide	15, 211 (1977)
Hycanthone and its mesylate	13, 91 (1977)
Hydralazine and its hydrochloride	24, 85 (1980) <i>Suppl.</i> 4, 135 (1982)
Hydrazine	4, 127 (1974) <i>Suppl.</i> 4, 136 (1982)
Hydrogen peroxide	36, 285 (1985)
Hydroquinone	15, 155 (1977)
4-Hydroxyazobenzene	8, 157 (1975)
17 α -Hydroxyprogesterone caproate	21, 399 (1979) (<i>corr.</i> 42, 259) <i>Suppl.</i> 4, 195 (1982)
8-Hydroxyquinoline	13, 101 (1977)
8-Hydroxysenkirkine	10, 265 (1976)

I

Indeno[1,2,3- <i>cd</i>]pyrene	3, 229 (1973) 32, 373 (1983)
IQ (2-Amino-3-methylimidazo[4,5- <i>f</i>]quinoline)	40, 261 (1986)
Iron and steel founding	34, 133 (1984)
Iron-dextran complex	2, 161 (1973) <i>Suppl.</i> 4, 145 (1982)
Iron-dextrin complex	2, 161 (1973) (<i>corr.</i> 42, 252)
Iron oxide	1, 29 (1972)
Iron sorbitol-citric acid complex	2, 161 (1973)
Isatidine	10, 269 (1976)
Isonicotinic acid hydrazide	4, 159 (1974) <i>Suppl.</i> 4, 146 (1982)
Isophosphamide	26, 237 (1981)
Isopropyl alcohol	15, 223 (1977) <i>Suppl.</i> 4, 151 (1982)
Isopropyl oils	15, 223 (1977) <i>Suppl.</i> 4, 151 (1982)
Isosafrole	1, 169 (1972) 10, 232 (1976)

J

Jacobine 10, 275 (1976)

K

Kaempferol 31, 171 (1983)

L

Lasiocarpine 10, 281 (1976)
Lauroyl peroxide 36, 315 (1985)
Lead and lead compounds 1, 40 (1972) (*corr.* 42, 251)
Lead acetate and its trihydrate 2, 52, 150 (1973)
Lead carbonate 23, 39, 205, 325 (1980)
Lead chloride *Suppl.* 4, 149 (1982)
Lead naphthenate
Lead nitrate
Lead oxide
Lead phosphate
Lead subacetate
Lead tetroxide
Tetraethyllead
Tetramethyllead
The leather goods manufacturing industry (other than boot and 25, 279 (1981)
shoe manufacture and tanning) *Suppl.* 4, 142 (1982)
The leather tanning and processing industries 25, 201 (1981)
Suppl. 4, 142 (1982)
Ledate 12, 131 (1976)
Light Green SF 16, 209 (1978)
Lindane 5, 47 (1974)
20, 196 (1979) (*corr.* 42, 258)
Suppl. 4, 133 (1982)
The lumber and sawmill industries (including logging) 25, 49 (1981)
Suppl. 4, 143 (1982)
Luteoskyrin 10, 163 (1976)
Lynoestrenol 21, 407 (1979)
Suppl. 4, 195 (1982)

M

Magenta 4, 57 (1974) (*corr.* 42, 252)
Suppl. 4, 152 (1982)
Malathion 30, 103 (1983)
Maleic hydrazide 4, 173 (1974) (*corr.* 42, 253)
Malonaldehyde 36, 163 (1985)
Maneb 12, 137 (1976)

CUMULATIVE INDEX

279

Mannomustine and its dihydrochloride	9, 157 (1975)
MCPCA (<i>see also</i> Chlorophenoxy herbicides, occupational exposures to)	<i>Suppl.</i> 4, 211 (1982) 30, 255 (1983)
MeA- α -C (2-Amino-3-methyl-9 <i>H</i> -pyrido[2,3- <i>b</i>]indole)	40, 253 (1986)
Medphalan	9, 168 (1975)
Medroxyprogesterone acetate	6, 157 (1974) 21, 417 (1979) (<i>corr.</i> 42, 259) <i>Suppl.</i> 4, 196 (1982) 21, 431 (1979) <i>Suppl.</i> 4, 198 (1982) 40, 275 (1986)
Megestrol acetate	
MeIQ (2-Amino-3,4-dimethylimidazo[4,5- <i>f</i>]quinoline)	
MeIQx (2-Amino-3,8-dimethylimidazo[4,5- <i>f</i>]quinoxaline)	40, 283 (1986)
Melamine	39, 333 (1986)
Melphalan	9, 167 (1975) <i>Suppl.</i> 4, 154 (1982) 26, 249 (1981) <i>Suppl.</i> 4, 155 (1982)
6-Mercaptopurine	9, 169 (1975) 6, 87 (1974) 21, 257 (1979) (<i>corr.</i> 42, 259) <i>Suppl.</i> 4, 188 (1982) 26, 267 (1981) <i>Suppl.</i> 4, 157 (1982) 24, 101 (1980) <i>Suppl.</i> 4, 158 (1982)
Merphalan	
Mestranol	
Methotrexate	
Methoxsalen	
Methoxychlor	5, 193 (1974) 20, 259 (1979)
5-Methoxypsoralen	40, 327 (1986)
Methyl acrylate	19, 52 (1979) 39, 99 (1986)
2-Methylaziridine	9, 61 (1975)
Methylazoxymethanol	10, 121 (1976)
Methylazoxymethanol acetate	1, 164 (1972) 10, 131 (1976)
Methyl bromide	41, 187 (1986)
Methyl carbamate	12, 151 (1976)
Methyl chloride	41, 161 (1986)
1-, 2-, 3-, 4-, 5- and 6-Methylchrysene	32, 379 (1983)
<i>N</i> -Methyl- <i>N</i> ,4-dinitrosoaniline	1, 141 (1972)
4,4'-Methylene bis(2-chloroaniline)	4, 65 (1974) (<i>corr.</i> 42, 252)
4,4'-Methylene bis(<i>N,N</i> -dimethyl)benzenamine	27, 119 (1982)
4,4'-Methylene bis(2-methylaniline)	4, 73 (1974)
4,4'-Methylenedianiline and its dihydrochloride	4, 79 (1974) (<i>corr.</i> 42, 252) 39, 347 (1986)

4,4'-Methylenediphenyl diisocyanate	19, 314 (1979)
2- and 3-Methylfluoranthenes	32, 399 (1983)
Methyl iodide	15, 245 (1977) 41, 213 (1986)
Methyl methacrylate	19, 187 (1979)
Methyl methanesulphonate	7, 253 (1974)
2-Methyl-1-nitroanthraquinone	27, 205 (1982)
N-Methyl- <i>N</i> '-nitro- <i>N</i> -nitrosoguanidine	4, 183 (1974)
3-Methylnitrosaminopropionaldehyde	37, 263 (1985)
3-Methylnitrosaminopropionitrile	37, 263 (1985)
4-(Methylnitrosamino)-4-(3-pyridyl)butanal (NNA)	37, 205 (1985)
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	37, 209 (1985)
Methyl parathion	30, 131 (1983)
1-Methylphenanthrene	32, 405 (1983)
7-Methylpyrido[3,4- <i>c</i>]psoralen	40, 349 (1986)
Methyl red	8, 161 (1975)
Methyl selenac	12, 161 (1976)
Methylthiouracil	7, 53 (1974)
Metronidazole	13, 113 (1977) <i>Suppl.</i> 4, 160 (1982)
Mineral oils	3, 30 (1973) <i>Suppl.</i> 4, 227 (1982) 33, 87 (1984) (<i>corr.</i> 42, 262)
Mirex	5, 203 (1974) 20, 283 (1979) (<i>corr.</i> 42, 258)
Mitomycin C	10, 171 (1976)
Modacrylic fibres	19, 86 (1979)
Monocrotaline	10, 291 (1976)
Monuron	12, 167 (1976)
5-(Morpholinomethyl)-3-[(5-nitro-furfurylidene)amino]-2-oxazolidinone	7, 161 (1974)
Mustard gas	9, 181 (1975) (<i>corr.</i> 42, 254) <i>Suppl.</i> 4, 163 (1982)
N	
Nafenopin	24, 125 (1980)
1,5-Naphthalenediamine	27, 127 (1982)
1,5-Naphthalene diisocyanate	19, 311 (1979)
1-Naphthylamine	4, 87 (1974) (<i>corr.</i> 42, 253) <i>Suppl.</i> 4, 164 (1982)
2-Naphthylamine	4, 97 (1974) <i>Suppl.</i> 4, 166 (1982)
1-Naphthylthiourea (ANTU)	30, 347 (1983)

CUMULATIVE INDEX

281

Nickel and nickel compounds	2, 126 (1973) (<i>corr.</i> 42, 252)
Nickel acetate and its tetrahydrate	11, 75 (1976)
Nickel ammonium sulphate	<i>Suppl.</i> 4, 167 (1982)
Nickel carbonate	
Nickel carbonyl	
Nickel chloride	
Nickel-gallium alloy	
Nickel hydroxide	
Nickelocene	
Nickel oxide	
Nickel subsulphide	
Nickel sulphate	
Niridazole	13, 123 (1977)
Nithiazide	31, 179 (1983)
5-Nitroacenaphthene	16, 319 (1978)
5-Nitro- <i>ortho</i> -anisidine	27, 133 (1982)
9-Nitroanthracene	33, 179 (1984)
6-Nitrobenzo[<i>a</i>]pyrene	33, 187 (1984)
4-Nitrobiphenyl	4, 113 (1974)
6-Nitrochrysene	33, 195 (1984)
Nitrofen	30, 271 (1983)
3-Nitrofluoranthene	33, 201 (1984)
5-Nitro-2-furaldehyde semicarbazone	7, 171 (1974)
1-[<i>(5</i> -Nitrofurylidene)amino]-2-imidazolidinone	7, 181 (1974)
<i>N</i> -[4-(5-Nitro-2-furyl)-2-thiazolyl]acetamide	1, 181 (1972) 7, 185 (1974)
Nitrogen mustard and its hydrochloride	9, 193 (1975) <i>Suppl.</i> 4, 170 (1982)
Nitrogen mustard <i>N</i> -oxide and its hydrochloride	9, 209 (1975)
2-Nitropropane	29, 331 (1982)
1-Nitropyrene	33, 209 (1984)
<i>N</i> -Nitrosatable drugs	24, 297 (1980) (<i>corr.</i> 42, 260)
<i>N</i> -Nitrosatable pesticides	30, 359 (1983)
<i>N'</i> -Nitrosoanabasine	37, 225 (1985)
<i>N'</i> -Nitrosoanatabine	37, 233 (1985)
<i>N</i> -Nitrosodi- <i>n</i> -butylamine	4, 197 (1974) 17, 51 (1978)
<i>N</i> -Nitrosodiethanolamine	17, 77 (1978)
<i>N</i> -Nitrosodiethylamine	1, 107 (1972) (<i>corr.</i> 42, 251) 17, 83 (1978) (<i>corr.</i> 42, 257)
<i>N</i> -Nitrosodimethylamine	1, 95 (1972) 17, 125 (1978) (<i>corr.</i> 42, 257)
<i>N</i> -Nitrosodiphenylamine	27, 213 (1982)
<i>para</i> -Nitrosodiphenylamine	27, 227 (1982) (<i>corr.</i> 42, 261)
<i>N</i> -Nitrosodi- <i>n</i> -propylamine	17, 177 (1978)
<i>N</i> -Nitroso- <i>N</i> -ethylurea	1, 135 (1972) 17, 191 (1978)

<i>N</i> -Nitrosoguvacine	37, 263 (1985)
<i>N</i> -Nitrosoguvacoline	37, 263 (1985)
<i>N</i> -Nitrosohydroxyproline	17, 304 (1978)
<i>N</i> -Nitrosomethylethylamine	17, 221 (1978)
<i>N</i> -Nitroso- <i>N</i> -methylurea	1, 125 (1972) 17, 227 (1978)
<i>N</i> -Nitroso- <i>N</i> -methylurethane	4, 211 (1974)
<i>N</i> -Nitrosomethylvinylamine	17, 257 (1978)
<i>N</i> -Nitrosomorpholine	17, 263 (1978)
<i>N</i> ² -Nitrosonornicotine	17, 281 (1978) 37, 241 (1985)
<i>N</i> -Nitrosopiperidine	17, 287 (1978)
<i>N</i> -Nitrosoproline	17, 303 (1978)
<i>N</i> -Nitrosopyrrolidine	17, 313 (1978)
<i>N</i> -Nitrososarcosine	17, 327 (1978)
Nitrovin	31, 185 (1983)
Noresthisterone and its acetate	6, 179 (1974) 21, 441 (1979) <i>Suppl.</i> 4, 199 (1982)
Norethynodrel	6, 191 (1974) 21, 46 (1979) (<i>corr.</i> 42, 259) <i>Suppl.</i> 4, 201 (1982)
Norgestrel	6, 201 (1974) 21, 479 (1979) <i>Suppl.</i> 4, 202 (1982)
Nylon 6	19, 120 (1979)
O	
Ochratoxin A	10, 191 (1976) 31, 191 (1983) (<i>corr.</i> 42, 262)
Oestradiol-17 β	6, 99 (1974) 21, 279 (1979) <i>Suppl.</i> 4, 190 (1982)
Oestradiol 3-benzoate	21, 281 (1979)
Oestradiol dipropionate	21, 283 (1979)
Oestradiol mustard	9, 217 (1975)
Oestradiol-17 β -valerate	21, 284 (1979)
Oestriol	6, 117 (1974) 21, 327 (1979)
Oestrone	6, 123 (1974) 21, 343 (1979) (<i>corr.</i> 42, 259) <i>Suppl.</i> 4, 191 (1982)
Oestrone benzoate	21, 345 (1979) <i>Suppl.</i> 4, 191 (1982)
Oil Orange SS	8, 165 (1975)

CUMULATIVE INDEX

283

Oral contraceptives	
combined	21, 103, 133 (1979) <i>Suppl.</i> 4, 173 (1982)
sequential	21, 111 (1979) <i>Suppl.</i> 4, 177 (1982)
Orange I	8, 173 (1975)
Orange G	8, 181 (1975)
Oxazepam	13, 58 (1977)
Oxymetholone	13, 131 (1977) <i>Suppl.</i> 4, 203 (1982)
Oxyphenbutazone	13, 185 (1977)
P	
Panfuran S (Dihydroxymethylfuratrizine)	24, 77 (1980)
Parasorbic acid	10, 199 (1976) (<i>corr.</i> 42, 255)
Parathion	30, 153 (1983)
Patulin	10, 205 (1976) 40, 83 (1986)
Penicillic acid	10, 211 (1976)
Pentachloroethane	41, 99 (1986)
Pentachlorophenol (<i>see also</i> Chlorophenols, occupational exposures to)	20, 203 (1979) <i>Suppl.</i> 4, 88, 205 (1982)
Perylene	32, 411 (1983)
Petasitenine	31, 207 (1983)
Phenacetin	3, 141 (1973) 24, 135 (1980) <i>Suppl.</i> 4, 47 (1982)
Phenanthrene	32, 419 (1983)
Phenazopyridine [2,6-Diamino-3-(phenylazo)pyridine] and its hydrochloride	8, 117 (1975) 24, 163 (1980) (<i>corr.</i> 42, 260) <i>Suppl.</i> 4, 207 (1982)
Phenelzine and its sulphate	24, 175 (1980) <i>Suppl.</i> 4, 207 (1982)
Phenicarbazide	12, 177 (1976)
Phenobarbital and its sodium salt	13, 157 (1977) <i>Suppl.</i> 4, 208 (1982) <i>Suppl.</i> 4, 211 (1982)
Phenoxyacetic acid herbicides (occupational exposure to) (<i>see also</i> Chlorophenoxy herbicides, occupational exposures to)	9, 223 (1975) 24, 185 (1980)
Phenoxybenzamine and its hydrochloride	13, 183 (1977) <i>Suppl.</i> 4, 212 (1982)
Phenylbutazone	16, 111 (1978) 16, 125 (1978)
<i>meta</i> -Phenylenediamine and its hydrochloride	
<i>para</i> -Phenylenediamine and its hydrochloride	

<i>N</i> -Phenyl-2-naphthylamine	16, 325 (1978) (<i>corr.</i> 42, 257)
<i>ortho</i> -Phenylphenol and its sodium salt	<i>Suppl.</i> 4, 213 (1982)
Phenytoin and its sodium salt	30, 329 (1983)
Piperazine oestrone sulphate	13, 201 (1977)
Piperonyl butoxide	<i>Suppl.</i> 4, 215 (1982)
Polyacrylic acid	21, 148 (1979)
Polybrominated biphenyls	30, 183 (1983)
Polychlorinated biphenyls	19, 62 (1979)
	18, 107 (1978)
	41, 261 (1986)
	7, 261 (1974)
	18, 43 (1978) (<i>corr.</i> 42, 258)
Polychloropropene	<i>Suppl.</i> 4, 217 (1982)
Polyethylene (low-density and high-density)	19, 141 (1979)
Polymethylene polyphenyl isocyanate	19, 164 (1979)
Polymethyl methacrylate	19, 314 (1979)
Polyoestradiol phosphate	19, 195 (1979)
Polypropylene	21, 286 (1979)
Polystyrene	19, 218 (1979)
Polytetrafluoroethylene	19, 245 (1979)
Polyurethane foams (flexible and rigid)	19, 288 (1979)
Polyvinyl acetate	19, 320 (1979)
Polyvinyl alcohol	19, 346 (1979)
Polyvinyl chloride	19, 351 (1979)
	7, 306 (1974)
	19, 402 (1979)
Polyvinyl pyrrolidone	19, 463 (1979)
Ponceau MX	8, 189 (1975)
Ponceau 3R	8, 199 (1975)
Ponceau SX	8, 207 (1975)
Potassium bis(2-hydroxyethyl)dithiocarbamate	12, 183 (1976)
Potassium bromate	40, 207 (1986)
Prednisone	26, 293 (1981)
	<i>Suppl.</i> 4, 219 (1982)
Procarbazine and its hydrochloride	26, 311 (1981)
	<i>Suppl.</i> 4, 220 (1982)
Proflavine and its salts	24, 195 (1980)
Progesterone	6, 135 (1974)
	21, 49 (1979) (<i>corr.</i> 42, 259)
Pronetalol hydrochloride	<i>Suppl.</i> 4, 202 (1982)
1,3-Propane sultone	13, 227 (1977) (<i>corr.</i> 42, 256)
Propham	4, 253 (1974) (<i>corr.</i> 42, 253)
β -Propiolactone	12, 189 (1976)
<i>n</i> -Propyl carbamate	4, 259 (1974) (<i>corr.</i> 42, 253)
Propylene	12, 201 (1976)
Propylene oxide	19, 213 (1979)
	11, 191 (1976)
	36, 227 (1985) (<i>corr.</i> 42, 263)

CUMULATIVE INDEX

285

Propylthiouracil	7, 67 (1974) <i>Suppl.</i> 4, 222 (1982)
Ptaquiloside (<i>see</i> Bracken fern)	
The pulp and paper industry	25, 157 (1981) <i>Suppl.</i> 4, 144 (1982)
Pyrene	32, 431 (1983)
Pyrido[3,4- <i>c</i>]psoralen	40, 349 (1986)
Pyrimethamine	13, 233 (1977)
Pyrrolizidine alkaloids	10, 333 (1976)
Q	
Quercetin (<i>see also</i> Bracken fern)	31, 213 (1983)
<i>para</i> -Quinone	15, 255 (1977)
Quintozene (Pentachloronitrobenzene)	5, 211 (1974)
R	
Reserpine	10, 217 (1976) 24, 211 (1980) (<i>corr.</i> 42, 260) <i>Suppl.</i> 4, 222 (1982)
Resorcinol	15, 155 (1977)
Retrorsine	10, 303 (1976)
Rhodamine B	16, 221 (1978)
Rhodamine 6G	16, 233 (1978)
Riddelliine	10, 313 (1976)
Rifampicin	24, 243 (1980)
The rubber industry	28 (1982) (<i>corr.</i> 42, 261) <i>Suppl.</i> 4, 144 (1982)
Rugulosin	40, 99 (1986)
S	
Saccharated iron oxide	2, 161 (1973)
Saccharin	22, 111 (1980) (<i>corr.</i> 42, 259) <i>Suppl.</i> 4, 224 (1982)
Safrole	1, 169 (1972) 10, 231 (1976)
Scarlet Red	8, 217 (1975)
Selenium and selenium compounds	9, 245 (1975) (<i>corr.</i> 42, 255)
Semicarbazide hydrochloride	12, 209 (1976) (<i>corr.</i> 42, 256)
Seneciphylline	10, 319 (1976)
Senkirkine	10, 327 (1976) 31, 231 (1983)
Sepiolite	42, 175 (1987)
Shale-oils	35, 161 (1985)
Shikimic acid (<i>see</i> Bracken fern)	
Silica	42, 39 (1987)

Sodium cyclamate	22, 56 (1980) <i>Suppl.</i> 4, 97 (1982)
Sodium diethyldithiocarbamate	12, 217 (1976)
Sodium equilin sulphate	21, 148 (1979)
Sodium oestrone sulphate	21, 147 (1979)
Sodium <i>ortho</i> -phenylphenate	30, 329 (1983)
Sodium saccharin	22, 113 (1980) <i>Suppl.</i> 4, 224 (1982)
Soots	3, 22 (1973) <i>Suppl.</i> 4, 227 (1982)
Spironolactone	35, 219 (1985) 24, 259 (1980) <i>Suppl.</i> 4, 229 (1982)
Sterigmatocystin	1, 175 (1972) 10, 245 (1976)
Streptozotocin	4, 221 (1974) 17, 337 (1978)
Styrene	19, 231 (1979) (<i>corr.</i> , 42, 258) <i>Suppl.</i> 4, 229 (1982)
Styrene-acrylonitrile copolymers	19, 97 (1979)
Styrene-butadiene copolymers	19, 252 (1979)
Styrene oxide	11, 201 (1976) 19, 275 (1979) <i>Suppl.</i> 4, 229 (1982)
Succinic anhydride	36, 245 (1985)
Sudan I	15, 265 (1977)
Sudan II	8, 225 (1975)
Sudan III	8, 233 (1975)
Sudan Brown RR	8, 241 (1975)
Sudan Red 7B	8, 249 (1975)
Sulfafurazole (Sulphisoxazole)	8, 253 (1975) 24, 275 (1980) <i>Suppl.</i> 4, 233 (1982)
Sulfallate	30, 283 (1983)
Sulfamethoxazole	24, 285 (1980) <i>Suppl.</i> 4, 234 (1982)
Sunset Yellow FCF	8, 257 (1975)
Symphtine	31, 239 (1983)
T	
2,4,5-T and esters (<i>see also</i> Chlorophenoxy herbicides, occupational exposures to)	15, 273 (1977) <i>Suppl.</i> 4, 211, 235 (1982)
Talc	42, 185 (1987)
Tannic acid	10, 253 (1976) (<i>corr.</i> 42, 255)
Tannins	10, 254 (1976)
Terpene polychlorinates (Strobane®)	5, 219 (1974)
Testosterone	6, 209 (1974) 21, 519 (1979)

CUMULATIVE INDEX

287

Testosterone oenanthate	21, 521 (1979)
Testosterone propionate	21, 522 (1979)
2,2',5,5'-Tetrachlorobenzidine	27, 141 (1982)
2,3,7,8-Tetrachlorodibenzo- <i>para</i> -dioxin (TCDD)	15, 41 (1977) <i>Suppl.</i> 4, 211, 238 (1982)
1,1,1,2-Tetrachloroethane	41, 87 (1986)
1,1,2,2-Tetrachloroethane	20, 477 (1979)
Tetrachloroethylene	20, 491 (1979) <i>Suppl.</i> 4, 243 (1982)
Tetrachlorvinphos	30, 197 (1983)
Tetrafluoroethylene	19, 285 (1979)
Thioacetamide	7, 77 (1974)
4,4'-Thiodianiline	16, 343 (1978) 27, 147 (1982)
Thiouracil	7, 85 (1974)
Thiourea	7, 95 (1974)
Thiram	12, 225 (1976)
Tobacco habits other than smoking	37 (1985) (<i>corr.</i> 42, 263)
Tobacco smoking	38 (1986) (<i>corr.</i> 42, 263-264)
Toluene diisocyanate	39, 287 (1986) (<i>corr.</i> 42, 264)
2,4-Toluene diisocyanate	19, 303 (1979) 39, 287 (1986)
2,6-Toluene diisocyanate	19, 303 (1979) 39, 287 (1986)
<i>ortho</i> -Toluenesulphonamide	22, 121 (1980) <i>Suppl.</i> 4, 224 (1982)
<i>ortho</i> -Toluidine and its hydrochloride	16, 349 (1978) 27, 155 (1982) <i>Suppl.</i> 4, 245 (1982)
Toxaphene (Polychlorinated camphenes)	20, 327 (1979)
Treosulphan	26, 341 (1981) <i>Suppl.</i> 4, 246 (1982)
Trichlorfon	30, 207 (1983)
1,1,1-Trichloroethane	20, 515 (1979)
1,1,2-Trichloroethane	20, 533 (1979)
Trichloroethylene	11, 263 (1976) 20, 545 (1979) <i>Suppl.</i> 4, 247 (1982)
2,4,5- and 2,4,6-Trichlorophenols (<i>see also</i> Chlorophenols, occupational exposures to)	20, 349 (1979) <i>Suppl.</i> 4, 88, 249 (1982)
Trichlorotriethylamine hydrochloride	9, 229 (1975)
T ₂ -Trichothecene	31, 265 (1983)
Triethylene glycol diglycidyl ether	11, 209 (1976)

2,4,5-Trimethylaniline and its hydrochloride	27, 177 (1982)
2,4,6-Trimethylaniline and its hydrochloride	27, 178 (1982)
4,5',8-Trimethylpsoralen	40, 357 (1986)
Triphenylene	32, 447 (1983)
Tris(aziridinyl)- <i>para</i> -benzoquinone (Triaziquone)	9, 67 (1975) <i>Suppl.</i> 4, 251 (1982)
Tris(1-aziridinyl)phosphine oxide	9, 75 (1975)
Tris(1-aziridinyl)phosphine sulphide (Thiotepa)	9, 85 (1975) <i>Suppl.</i> 4, 252 (1982)
2,4,6-Tris(1-aziridinyl)- <i>s</i> -triazine	9, 95 (1975)
1,2,3-Tris(chloromethoxy)propane	15, 301 (1977)
Tris(2,3-dibromopropyl)phosphate	20, 575 (1979)
Tris(2-methyl-1-aziridinyl)phosphine oxide	9, 107 (1975)
Trp-P-1 [3-Amino-1,4-dimethyl-5 <i>H</i> -pyrido[4,3- <i>b</i>]indole] and its acetate	31, 247 (1983)
Trp-P-2 [3-Amino-1-methyl-5 <i>H</i> -pyrido[4,3- <i>b</i>]indole] and its acetate	31, 255 (1983)
Trypan blue	8, 267 (1975)

U

Ultraviolet radiation	40, 379 (1986)
Uracil mustard	9, 235 (1975) <i>Suppl.</i> 4, 256 (1982)
Urethane	7, 111 (1974)

V

Vinblastine sulphate	26, 349 (1981) (<i>corr.</i> 42, 261) <i>Suppl.</i> 4, 257 (1982)
Vincristine sulphate	26, 365 (1981) <i>Suppl.</i> 4, 259 (1982)
Vinyl acetate	19, 341 (1979)
Vinyl bromide	39, 113 (1986) 19, 367 (1979)
Vinyl chloride	39, 133 (1986) 7, 291 (1974) 19, 377 (1979) (<i>corr.</i> 42, 258) <i>Suppl.</i> 4, 260 (1982)
Vinyl chloride-vinyl acetate copolymers	7, 311 (1976) 19, 412 (1979)
4-Vinylcyclohexene	11, 277 (1976) 39, 181 (1986)
Vinyl fluoride	39, 147 (1986)
Vinyldene chloride	19, 439 (1979) <i>Suppl.</i> 4, 262 (1982) (<i>corr.</i> 31, 293) 39, 195 (1986)

CUMULATIVE INDEX

289

Vinylidene chloride-vinyl chloride copolymers	19, 448 (1979) (<i>corr.</i> 42, 258)
Vinylidene fluoride	39, 227 (1986)
N-Vinyl-2-pyrrolidine	19, 461 (1979)
W	
Wollastonite	42, 145 (1987)
X	
2,4-Xylidine and its hydrochloride	16, 367 (1978)
2,5-Xylidine and its hydrochloride	16, 377 (1978)
Y	
Yellow AB	8, 279 (1975)
Yellow OB	8, 287 (1975)
Z	
Zearalenone	31, 279 (1983)
Zectran	12, 237 (1976)
Zineb	12, 245 (1976)
Ziram	12, 259 (1976)

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Exhibit 27



WORLD HEALTH ORGANIZATION

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**IARC MONOGRAPHS
ON THE
EVALUATION OF THE CARCINOGENIC
RISKS TO HUMANS**

**Overall Evaluations of Carcinogenicity: An Updating
of *IARC Monographs* Volumes 1 to 42**

SUPPLEMENT 7

LYON, FRANCE

1987

⁵⁰Katsnelson, B.A., Neizvestnova, Y.M. & Blokhin, V.A. (1986) Stomach carcinogenesis induction by chronic treatment with arsenic (Russ.). *Vopr. Onkol.*, 32, 68-73

⁵¹Pershagen, G. & Björklund, N.-E. (1985) On the pulmonary tumorigenicity of arsenic trisulfide and calcium arsenate in hamsters. *Cancer Lett.*, 27, 99-104

⁵²Shirachi, D.Y., Johansen, M.G., McGowan, J.P. & Tu, S.-H. (1983) Tumorigenic effect of sodium arsenite in rat kidney. *Proc. West. pharmacol. Soc.*, 26, 413-415

⁵³*IARC Monographs, Suppl.* 6, 71-76, 1987

ASBESTOS* (Group 1)

A. Evidence for carcinogenicity to humans (*sufficient*)

Numerous reports from several countries have described cases or series of pleural and peritoneal mesotheliomas in relation to occupational exposure to various types and mixtures of asbestos (including talc containing asbestos), although occupational exposures have not been identified in all cases¹⁻²¹. Mesotheliomas of the tunica vaginalis testis and of the pericardium have been reported in persons occupationally exposed to asbestos²²⁻²⁴.

Environmental exposure either in the houses of asbestos workers or in the neighbourhood of asbestos mines or factories has been noted in some of the cases^{1,2,4-6,9,11,25,26}. It has been estimated that a third of the mesotheliomas occurring in the USA may be due to nonoccupational exposure²⁷. In a study from Israel, the incidence of mesothelioma was found to be higher among those born in the USA or in Europe relative to those born in Israel⁹.

In some of these case reports and in other studies, asbestos fibres were identified in the lung^{5,6,11,28-32}. Amphibole fibres usually predominated, but in a few cases mainly or only chrysotile fibres were found^{6,28}.

The long latency required for mesothelioma to develop after asbestos exposure has been documented in a number of publications^{11,13,26,28,33-37}. An increasing proportion of cases has been seen with increasing duration of exposure³⁶.

A number of epidemiological studies of respiratory cancer and mesothelioma have been reported in relation to exposure to unspecified or complex mixtures of asbestos in shipyard work³⁸⁻⁴⁵. The risk ratio for lung cancer has usually been moderately increased, both in these studies and in studies on various other occupational groups with similarly job-related but unspecified or complex asbestos exposures^{35,46-54}. Risk ratios of about 2-5 have been reported in some studies, but the ratio was considerably higher in one rather small study⁵⁵ and did not exceed unity in another⁴². In one study, individuals suffering from asbestosis had a considerably greater risk for lung cancer, with a risk ratio of 9.0⁵⁶. In some of the studies referred to, a number of mesotheliomas were also observed^{41,42,44,47,51,53,55}. Abdominal mesotheliomas have sometimes been mistaken for pancreatic cancer⁵⁷. Mesothelioma cases have been observed to have a relatively lower fibre content in the lungs than lung cancer cases³².

*Actinolite, amosite, anthophyllite, chrysotile, crocidolite, tremolite

Laryngeal cancer has been considered in two case-control studies, resulting in risk ratios of 2.4 and 2.3 that relate to shipyard work and unspecified exposure, respectively^{40,58}. A cohort study of insulation workers showed a relative risk of 1.9, based on nine cases⁵⁷. A case series indicated a high frequency of exposure to asbestos, especially in low-grade smokers⁵⁹. A risk ratio of 3.2 for laryngeal cancer was reported among chrysotile miners in an area with generally high incidence⁶⁰, but no increased risk was seen in a cohort of workers with exposure to crocidolite⁶¹. Two correlation studies have also indicated a relationship between laryngeal cancer and exposure to asbestos^{39,62}.

Mesotheliomas related to shipyard work and other exposures, including household contact with asbestos workers, have also been subject to epidemiological studies^{36,63-67}, resulting in risk ratios of about 3-15 in comparison with background rates not clearly referable to asbestos exposure.

Some studies have specifically considered environmental exposures with reference to mesotheliomas^{66,67}. Three correlation studies and one case-control study considering exposure to piped drinking-water⁶⁸⁻⁷¹ did not show consistently increased risks for any type of cancer, whereas another study⁷² considering chrysotile contamination mainly from natural sources gave some indication of an increase in the incidence of peritoneal and stomach cancers in persons of each sex, although no other cancer site was consistent in this respect.

Exposure to crocidolite has been studied with regard to risk of lung cancer^{61,73-76}, and risk ratios of about 2-3 have been reported. Three lung cancers and two mesotheliomas occurred in 20 individuals after one year of high exposure to crocidolite; at least 17 of the cases had asbestos-induced lung changes on X-ray films⁷⁷.

One study⁷⁸ of histological types of lung cancers showed that among persons exposed to crocidolite 45.7% of cases were squamous-cell carcinomas, as compared to 35.2% among unexposed persons. In the context of unspecified and complex exposures, small-cell carcinoma was found to be relatively more prevalent than other forms⁵⁰.

Exposure to chrysotile was found in some studies to result in virtually no increase in risk ratio^{60,79-81}, or a slightly elevated relative risk of lung cancer⁸²⁻⁸⁶. Somewhat higher risk ratios, up to 2.5, 3.5 and 2, respectively, were obtained in one study of chrysotile miners⁸⁷ and in two independent studies from one asbestos [chrysotile] textile plant^{88,89}, the latter being the more comprehensive. With regard to mesotheliomas, one study suggested a particularly high risk of combined exposure to chrysotile and amphiboles (risk ratio, 61), thus almost multiplying the risk ratios (6 and 12, respectively) of exposures to chrysotile and to amphiboles alone⁹⁰. Another study showed no mesothelioma among a large worker population with exposure to chrysotile only⁹¹.

A slight excess of lung cancer and some mesotheliomas appeared in some groups with mixed exposures involving amosite, chrysotile and crocidolite⁹²⁻⁹⁴. Exposure predominantly to amosite, but also to chrysotile, was reported to be the probable cause of at least four of five mesotheliomas (one peritoneal) observed in a UK insulation-board factory⁹⁵. One cohort with exposure to cummingtonite-grunerite, which is closely related to amosite, had no clear excess of lung cancer, although one case of mesothelioma was observed⁹⁶.

Exposure to tremolite and actinolite has been the subject of a few studies in investigations of vermiculite mining and milling^{97,98} and environmental exposure⁹⁹. The studies of miners indicated a risk ratio for lung cancer of up to approximately six fold. Deaths from mesothelioma were found in the occupational studies, whereas the study of environmental exposure showed no increased risk, although pleural plaques were reported. Publication of one case report of a mesothelioma after environmental exposure suggests that tremolite was of etiological importance³¹.

Cancers other than of the lung or mesothelioma have been considered in many studies^{1,17,35,39,41–44,48,51,55,60–62,68–70,72–74,76,83,87,89,92,93,96,97,99–108}. Some indicated an approximately two-fold risk with regard to gastrointestinal cancer in connection with shipyard work^{41,43}, and some increased risk was also seen in association with exposure to both chrysotile and crocidolite¹⁰³, to crocidolite^{61,74} or to chrysotile⁸⁷. Cancer of the colon and rectum was associated with asbestos exposure during chrysotile production, with an approximately two-fold risk⁸⁷; a similar excess was found for unspecified asbestos exposure¹⁰⁴. Some excess of ovarian cancer has been reported in two studies^{73,76} but not in another⁹²; exposure to crocidolite was probably more predominant in the studies that showed excesses. Bile-duct cancer appeared in excess in one study based on record-linking¹⁰⁵, and large-cell lymphomas of the gastrointestinal tract and oral cavity appeared to be strongly related to asbestos exposure in one small study covering 28 cases and 28 controls, giving a risk ratio of 8; however, ten cases and one control also had a history of malaria¹⁰⁶. An excess of lymphopoietic and haematopoietic malignancies has been reported in plumbers, pipe-fitters, sheet-metal workers and others with asbestos exposure^{17,54,107,108}.

The relationship between asbestos exposure and smoking indicates a synergistic effect of smoking with regard to lung cancer¹. Further evaluations indicate that this synergistic effect is close to a multiplicative model^{52,109}. As noted previously¹, the risk of mesothelioma appears to be independent of smoking^{47,66}, and a significantly decreasing trend in risk was observed with the amount smoked in one study⁶⁵.

The studies of the carcinogenic effect of asbestos exposure, including evidence reviewed earlier¹, show that occupational exposure to chrysotile, amosite and anthophyllite asbestos and to mixtures containing crocidolite results in an increased risk of lung cancer, as does exposure to minerals containing tremolite and actinolite and to tremolitic material mixed with anthophyllite and small amounts of chrysotile. Mesotheliomas have been observed after occupational exposure to crocidolite, amosite, tremolitic material and chrysotile asbestos. Gastrointestinal cancers occurred at an increased incidence in groups occupationally exposed to crocidolite, amosite, chrysotile or mixed fibres containing crocidolite, although not all studies are consistent in this respect. An excess of laryngeal cancer has also been observed in some groups of exposed workers. No clear excess of cancer has been associated with the presence of asbestos fibres in drinking-water. Mesotheliomas have occurred in individuals living in the neighbourhood of asbestos factories and mines and in people living with asbestos workers.

B. Evidence for carcinogenicity to animals (*sufficient*)

Asbestos has been tested for carcinogenicity by inhalation in rats, by intrapleural administration in rats and hamsters, by intraperitoneal injection in mice, rats and hamsters and by oral administration in rats and hamsters. Chrysotile, crocidolite, amosite, anthophyllite and tremolite produced mesotheliomas and lung carcinomas in rats after inhalation^{1,110,111} and mesotheliomas following intrapleural administration^{1,112}. Chrysotile, crocidolite, amosite and anthophyllite induced mesotheliomas in hamsters following intrapleural administration¹. Intraperitoneal administration of chrysotile, crocidolite and amosite induced peritoneal tumours, including mesotheliomas, in mice^{1,113} and rats^{1,111,114}. Given by the same route, crocidolite produced abdominal tumours in hamsters¹¹⁵, and tremolite and actinolite produced abdominal tumours in rats^{110,116-118}. A statistically significant increase in the incidence of malignant tumours was observed in rats given filter material containing chrysotile orally¹. In more recent studies, tumour incidence was not increased by oral administration of amosite or tremolite in rats¹¹⁹, of amosite in hamsters^{120,121} or of chrysotile in hamsters¹²¹. In two studies in rats, oral administration of chrysotile produced a low incidence of benign adenomatous polyps of the large intestine in males (9/250 *versus* 3/254 pooled controls)¹²² and of mesenteric haemangiomas (4/22 *versus* 0/47 controls)¹²³. Synergistic effects were observed following intratracheal administration of chrysotile and benzo[a]pyrene to rats and hamsters¹ and of intratracheal administration of chrysotile and subcutaneous or oral administration of *N*-nitroso-diethylamine to hamsters¹²⁴.

C. Other relevant data

Insulation workers exposed to asbestos 'displayed a marginal increase' in the incidence of sister chromatid exchanges in lymphocytes in one study¹²⁵.

Chrysotile did not induce micronuclei in bone-marrow cells of mice or chromosomal aberrations in bone-marrow cells of rhesus monkeys treated *in vivo*. In cultured human cells, conflicting results were reported for the induction of chromosomal aberrations and negative results for the induction of sister chromatid exchanges by chrysotile and crocidolite; amosite and crocidolite did not induce DNA strand breaks, and crocidolite was not mutagenic. Amosite, anthophyllite, chrysotile and crocidolite induced transformation of Syrian hamster embryo cells, chrysotile and crocidolite transformed BALB/c 3T3 mouse cells, and chrysotile transformed rat mesothelial cells. Neither amosite nor crocidolite transformed CH3 10T1/2 cells. In cultured rodent cells, amosite, anthophyllite, chrysotile and crocidolite induced chromosomal aberrations, and amosite, chrysotile and crocidolite induced sister chromatid exchanges; chrysotile and crocidolite induced aneuploidy and micronuclei. Chrysotile induced unscheduled DNA synthesis in rat hepatocytes. Amosite, chrysotile and crocidolite were inactive or weakly active in inducing mutation in rodent cells *in vitro*; none was mutagenic to bacteria¹²⁵.

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